Chapter 6
Surface-Bound Molecular Motors

In this chapter the efforts to prepare a surface-bound molecular motor are described. Especially for information storage technology, the ability to manipulate matter at the nanoscale would cause a major revolution. To use the molecular motors as components in these technologies, they need to be attached to a surface in order to be able to exert a force onto other nanotechnological components to perform work. A molecular motor with two legs was synthesized and successfully attached to the surface of gold colloids. The unidirectional rotation on the surface of this gold colloid was demonstrated by UV-Vis and CD spectroscopy. Further evidence for unidirectional rotation was obtained by demonstration of the rotary cycle with a deuterated derivative of the motor molecule. Furthermore, the gold colloids were investigated by transmission electron microscopy, dynamic light scattering and infrared spectroscopy. It appears that the molecular motor functions in the same way on the surface of the gold colloids as in solution.

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6.1 Introduction and Molecular Design

Nanotechnology is expected to cause a major revolution especially in information storage technology. Major efforts towards nanotechnological devices focus on the development of electronic systems of nano-dimensions and applications for data storage.[1] Problems with the current top-down approach can, however, be envisioned as silicon-based technology eventually reaches its limits. The alternative, bottom-up contruction of molecular devices has only recently come under investigation and is still in its infancy, but a number of prototypes of these machines have been constructed and have been shown to function at the molecular level (see chapter 1). In a future molecular machine, a molecular motor or a molecule that is able to perform a repetitive motion would be a key component. Control over motion of the molecule is a key feature in all these systems. Two prototype molecular motors, driven respectively by chemical energy[2] and light,[3] were simultaneously reported in 1999. The concept of the molecular motor developed in our group was further elaborated by introduction of the second-generation of molecular motors[4] and the introduction of a five-membered ring in the motor molecule.[5] The first-generation motor and the prototype sulfur bridged second-generation motor suffer from the fact that substantial heating is required for unidirectional rotation to occur at a reasonable rate. Much effort has been devoted to speed up the molecular motor. A five-membered ring analogue of the first generation motor and a whole range of different second-generation motors, where the rotation speed could be tuned in such a way that it allows unidirectional rotation at room temperature, have been designed, synthesized and studied. The versatile design of especially the second-generation molecular motor allows the development of differently substituted analogues which can be used for optimization of the molecular properties of these systems.

A logical next step for the development of molecular machinery is to use these molecular motors to drive a mechanical process. This can be accomplished by assembly to form large aggregates or mounting the motor system onto surfaces. In both cases the unidirectional rotation around the double bond should still be possible. Mounting of molecular devices onto a surface has been performed already by, for example, the groups of Sauvage, Tour, Balzani, Stoddart and Zink as is described in chapter 1.

For the study of behavior of molecules on surfaces, nanoparticles are a particularly attractive alternatives. Their properties reflect that of the surface, but also can be tuned by controlling, for example, the size of the particle and unlike surfaces, their behavior can be investigated in solution by UV-Vis and CD spectroscopy (figure 6.1). Moreover, gold nanoparticles have been studied well in the past[6] and have been shown to be applicable as a scaffolds and building blocks for the construction of macromolecular devices.[7] Furthermore, gold nanoparticles are easily functionalized with a large number of organic chromophores[8] and some photochromic molecular switches have been demonstrated to function while mounted on nanoparticles.[9,10,11] This shows that a motor molecule attached to a gold nanoparticle should be able to function as well. The approach taken in this research was based on the well-defined and strong interaction between thiols and gold. We designed a target system **6.1** composed of a gold nanoparticle functionalized with a molecular motor via a spacer with two thiol moieties to allow fixation of one half of the sterically overcrowded alkene.

The first and second-generation light-driven unidirectional molecular motors based on sterically overcrowded alkenes, as is described in the first three chapters of this thesis, are able to perform a unidirectional rotation around the central double bond. Driven by light, one half of a sterically overcrowded alkene, the rotor moiety, rotates in a single direction relative to the other half of the molecule, the stator. Crucial factors for the unidirectional process to proceed are the intrinsic helical shape of the molecule and the presence of one or two stereogenic centers. Two energetically uphill photo-isomerization steps each followed by a thermal helix inversion result in a full 360° unidirectional rotation around the central double bond. The system presented in this chapter is based on the dimethoxy substituted overcrowded alkene **6.2** which functions as a model compound in all the experiments performed (figure 6.1).

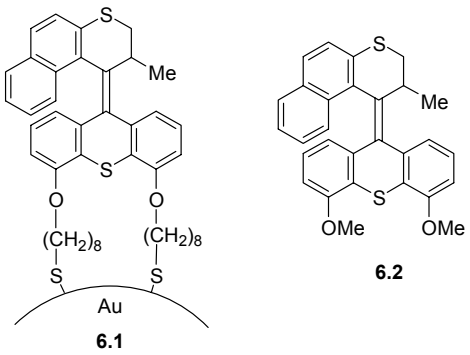
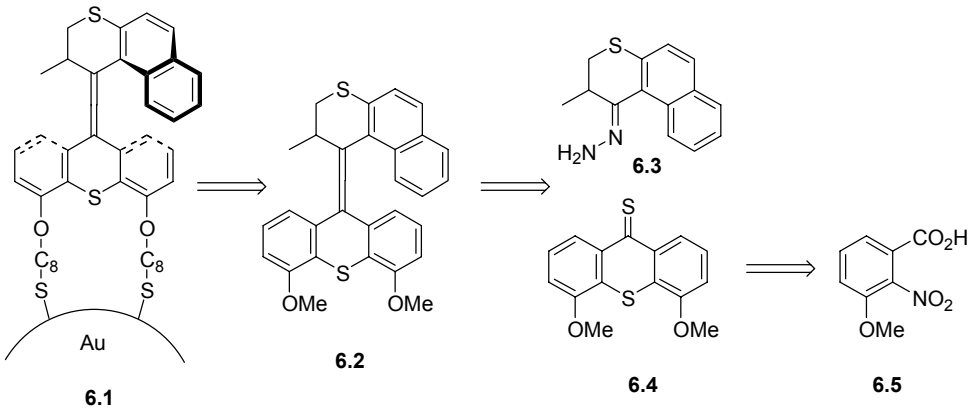


Figure 6.1 *Target compounds: motor functionalized gold colloid **6.1** and the dimethoxy substituted molecular motor **6.2**.*

Both target compounds **6.1** and **6.2** bear a bridging sulfur atom in the upper and the lower half of the molecule. Similar sulfur-bridged molecular motors were already known to require substantial heating in order for the unidirectional rotation to occur (see chapter 1 for an introduction). For continuous unidirectional rotation and for the compounds to perform work, this is an undesirable property. However, for the present investigation it allows the demonstration of the distinct stages of the molecular rotation at room temperature, which greatly facilitates the experiments and allows proof of the unidirectional rotation. A spacer of eight carbon atoms was chosen because a) it should have sufficient length to diminish direct (electronic) interaction between the chromophores and the gold surface, which might influence the photochemical processes to a considerable extent and to give the separate photochromic moieties of the motor the free volume required to perform the anticipated rotary motion and b) the tail should be short enough to prevent back-folding of the chromophores of the motor moieties towards the gold surface, which would also result in direct interaction between the chromophores and the metal core of the particle. Surface attachment of the motor molecule through two legs fixates the lower half of the molecule. In this way, the rotary motion of the upper half can be directed to generate a torque applicable in nanotechnological devices.

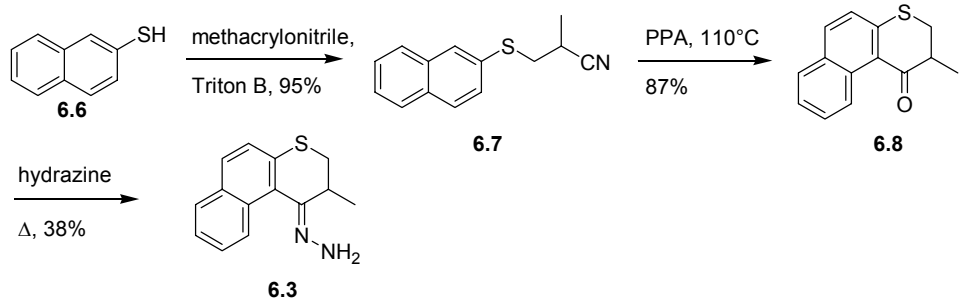
6.2 Synthesis

In the retrosynthesis of a gold nanoparticle functionalized with a molecular motor (scheme 6.1), three important aspects have to be taken into account. First of all, a platform is required onto which the two tails needed for linkage to a surface or colloid can be attached. Secondly, all molecular motor suffer from the often troublesome Barton-Kellogg coupling reaction. Therefore this reaction should be performed as late as possible in the synthesis sequence. Finally, since enantiomerically pure material is required for the CD measurements, the separation of enantiomers has to be performed also in a late stage of the synthesis.



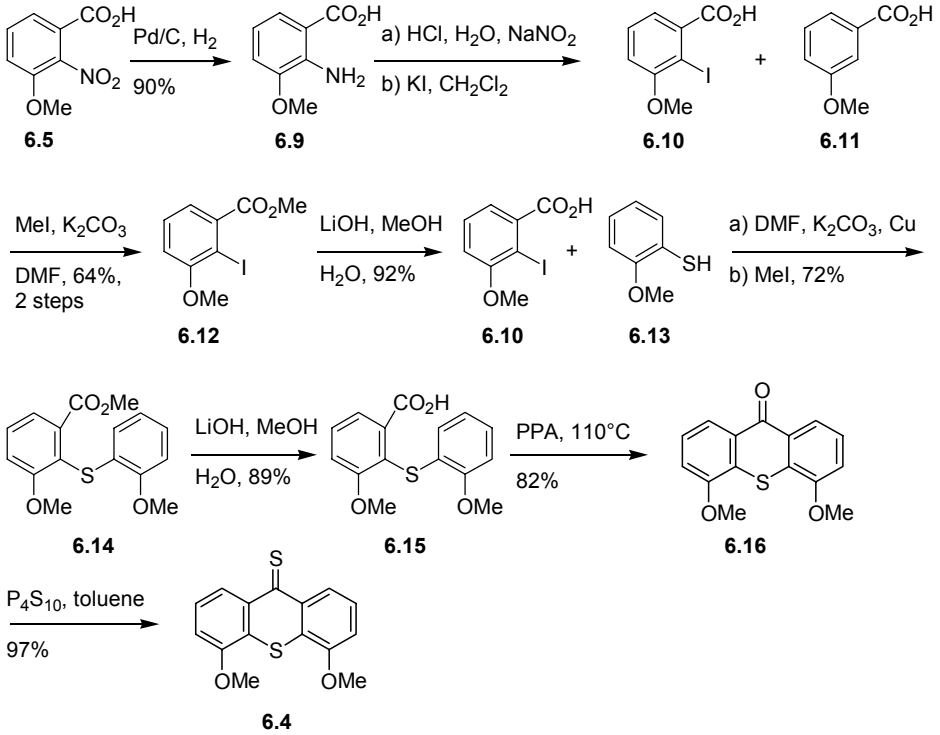
Scheme 6.1 *Retrosynthesis of the surface-bound molecular motor.*

The synthesis of the upper half of the molecule, with the hydrazone functionality needed for the Barton-Kellogg reaction, has been performed previously following a three step sequence starting from thionaphthol as shown in scheme 6.2. The first step is a Michael-addition of thionaphthol **6.6** to methacrylonitrile yielding **6.7**, which is then allowed to react further with PPA to give the ring-closed product **6.8**. The hydrazone **6.3** can be obtained in moderate yield from this ketone by heating at reflux overnight in a mixture of hydrazine and ethanol.



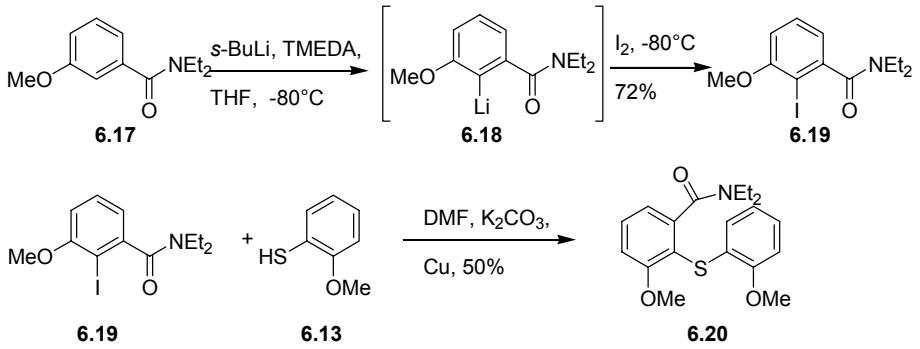
Scheme 6.2 *Synthesis of hydrazone **6.3**.*

The synthesis of the thioketone **6.4** required for the lower half is quite complicated, especially due to the 1,2,3-trisubstitution pattern in one of the arene building blocks needed. The initial synthesis of the lower part of the molecule was started with 3-methoxy-2-nitro-benzoic acid **6.5**, which was reduced using palladium on carbon under atmospheric hydrogen pressure to the amine **6.9**. Reaction of the amine with $NaNO_2$ following a Sandmeyer-like procedure and subsequent reaction with potassium iodide gave the iodide **6.10**. However, during the reaction, the product was partially reduced to form 3-methoxybenzoic acid **6.11**. The crude mixture of acids was converted to the methyl esters by reaction with methyl iodide in DMF in the presence of K_2CO_3. These esters could be separated by column chromatography to give the pure ester **6.12**, which was deprotected using a mixture of lithium hydroxide, methanol and water providing acid **6.10** in good yield. The Ullmann reaction, performed with acid **6.10** and 2-methoxybenzenethiol **6.13**, in the presence of copper powder and base in DMF, followed by esterification with methyl iodide, gave a complex reaction mixture from which was isolated after esterification methyl ester **6.14**. The methyl ester was then hydrolyzed using similar conditions as for acid **6.15**. A ring closure to ketone **6.16** using a Friedel-Crafts reaction was performed by treating the acid **6.15** with PPA at 110°C for 3h. Finally, the ketone **6.16** was converted by reaction with P_4S_{10} in refluxing toluene to the thioketone **6.4**, needed for the Barton-Kellogg reaction.



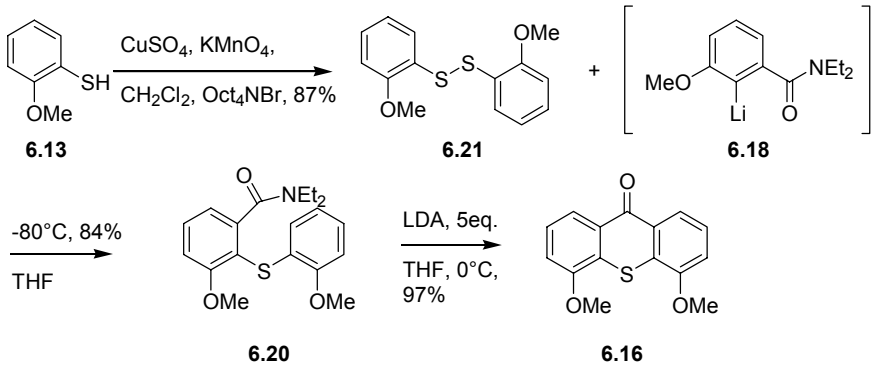
Scheme 6.3 *Classical synthetic approach to thioketone **6.4**.*

The synthesis of the lower part of the molecule suffers from a long synthetic sequence and a number of steps which proceed with variable yields. Therefore, a shorter reaction sequence was designed based on methodology developed by Snieckus.[12] In the first step, 3-methoxybenzoic acid is smoothly converted to amide **6.17** in high yield. Subsequently, by metallation with a complex of TMEDA and *s*-BuLi, intermediate **6.18** was generated which could be converted by reaction with molecular iodine into **6.19** in 72% yield. The subsequent Ullmann reaction using 2-methoxybenzenethiol **6.13** in combination with copper powder and K_2CO_3 gave the desired amide **6.20** in modest yield.



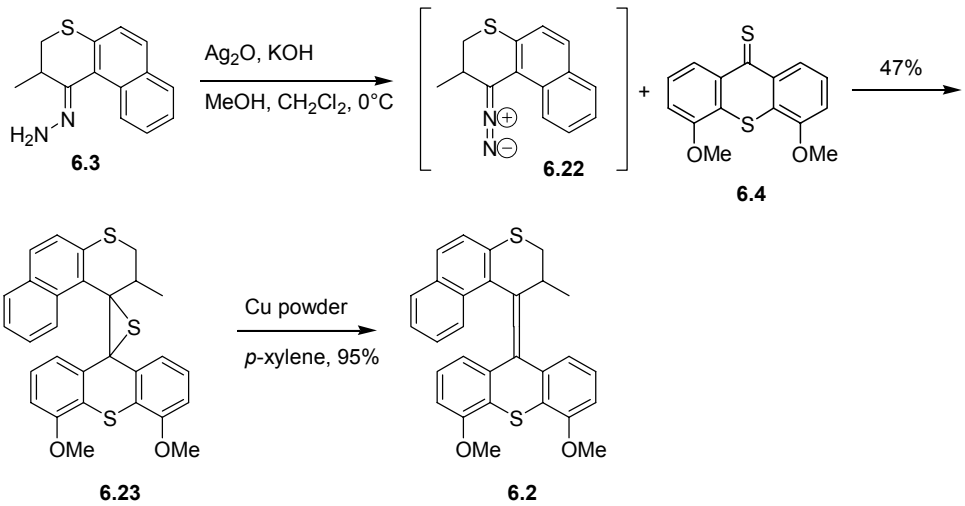
Scheme 6.4 *Synthesis of **6.16** using Snieckus' ortholithiation methodology.*

A more efficient way of synthesizing this amide, is by reaction of the lithiated intermediate **6.18** with the disulfide **6.21**. This disulfide **6.21** was prepared from the parent thiol **6.13** in good yield folllowing a literature procedure.[13] From an economic point of view, this reaction is less atom efficient since only half of relatively expensive sulfide **6.13** is incorporated into the molecule. From a synthetic point of view, however, two mediocre steps have been replaced with one reaction that gives high yields. With the amide **6.20** in hand, an anionic Friedel-Crafts reaction was performed by treatment of **6.20** with excess LDA according to methodology described by Snieckus *et al.*[14] This reaction is driven by a complex induced proximity effect and provides mild reaction conditions for these types of conversions, which are normally performed in pure sulfuric acid or PPA. In conclusion, the synthetic sequence featuring two subsequent metallations is much more efficient and less labor intensive than the originally designed procedures presented above. It provides the desired ketone **6.16** starting from 3-methoxybenzoic acid in only three, high yield steps in an overall yield of 75%.



Scheme 6.5 *Efficient three step procedure to ketone **6.16**.*

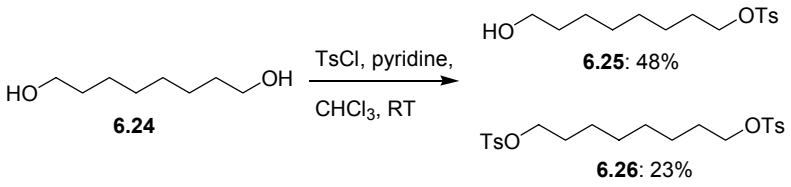
With efficient methodology to synthesize both the upper half **6.3** and lower half **6.4** in hand, both fragments are coupled using the Barton-Kellogg reaction. The hydrazone **6.3** was therefore oxidized using Ag_2O in combination with a saturated solution of KOH in methanol and $MgSO_4$ in dichloromethane. It has to be mentioned that the outcome of this reaction is highly unpredictable and often proceeds poorly. The deeply-red colored solution of the diazo compound **6.22** was allowed to react *in situ* with the thioketone **6.4**. The intermediate thiadiazoline was not observed as product, undoubtedly because during the reaction nitrogen evolution can be observed leading to the episulfide **6.23** in moderate yield. The episulfide can then easily be converted by reaction with copper powder to the alkene **6.2**.



Scheme 6.6 *Formation of the central double bond and synthesis of **6.2**.*

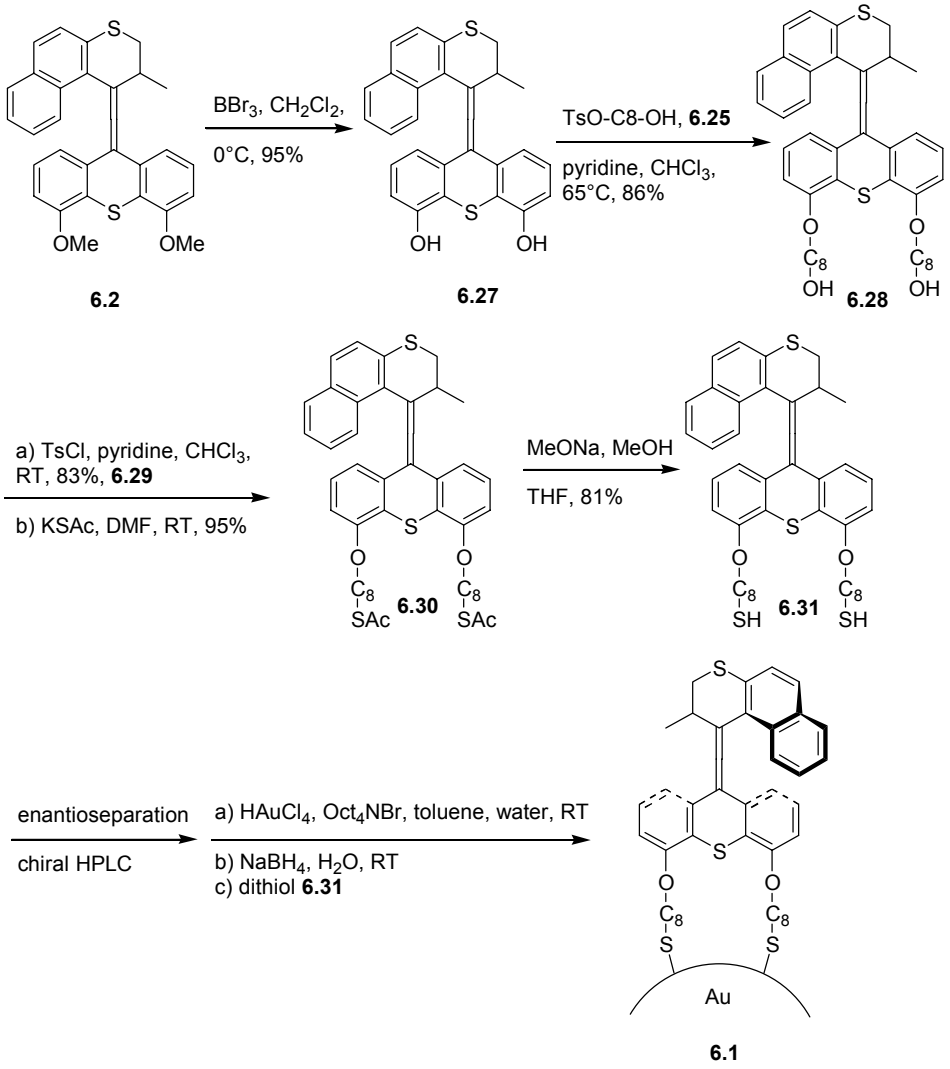
Having completed the synthesis of molecular motor **6.2**, the two legs for assembly on a surface need to be attached. The required eight carbon spacer **6.25** with an eight carbon

spacer was prepared from 1,8-octanediol and tosyl chloride as is shown in scheme 6.7. Deprotection of the two methoxy moieties of **6.2** was performed with BBr_3 in CH_2Cl_2 to give diphenol **6.27**. Spacer **6.25** was then allowed to react with the diphenol to give the motor molecule **6.28** (scheme 6.8).



Scheme 6.7 *Synthesis of the carbon spacer **6.25**.*

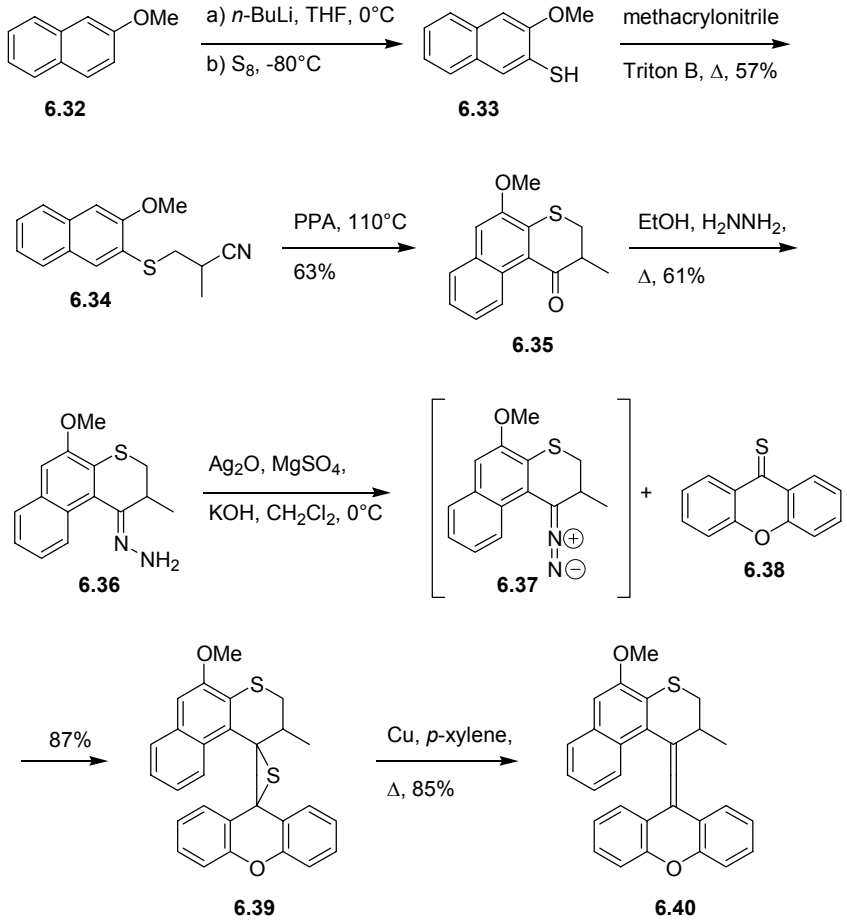
Further manipulation of the spacers was performed by conversion to the ditosylate **6.29** by tosyl chloride and pyridine in DMF. Nucleophilic substitution with of two thioacetic acid moieties yielded the motor **6.30**. Fortunately, in this very late state of the synthesis, the motor **6.30** could be separated into its enantiomers by preparative chiral HPLC. The enantiomerically pure dithioacetate **6.30** was then deprotected using sodium methoxide in a mixture of methanol and THF to give the dithiol **6.31**. This dithiol is then used directly in the synthesis of the colloids **6.1** to avoid possible oxidation of the thiol moieties by air. Finally, in the last step, the motor molecule is mounted on the gold colloid following the procedure described in the literature referred commonly to as the Brust-Schiffrin method.[15] Despite only small amounts of enantiomerically pure dithiol **6.31** available and the small scale of the reaction, the reaction proceeded analogous to those described in the literature for octanethiol and dodecanethiol.



Scheme 6.8 *Functionalization of the motor molecule and mounting onto the gold colloid.*

Of course, functionalization of the molecular motor is not only possible in the lower half of the molecule, but also in the upper half substituents could be introduced, which would allow further functionalization. The position of such a substituent should naturally not interfere with the rotary motion of the molecule and hence substitition at $C_{9'}$ and $C_{10'}$ is not suitable (see figure 6.2 for the numbering the upper half). The $C_{6'}$ and $C_{7'}$ position are synthetically very difficult to access, leaving $C_{5'}$ and $C_{8'}$ open for modication. Since of these two the $C_{5'}$ position can be most easily accessed, synthetic efforts were directed in this direction (scheme 6.8). The synthesis started with 2-methoxynaphthalene **6.32**, which

was lithiated at 0°C in THF. Reaction with elemental sulfur and workup gave the thiol **6.33** as a 10:1 mixture of two isomers that was directly used in the subsequent Michael addition to give **6.34** in reasonable yield. Due to the presence of the isomeric thiol, after reaction another isomer of the methacrylonitrile adduct was obtained, which somewhat complicated the purification of **6.34**. Ring closure of the nitrile **6.34** proceeded in moderate yields to give ketone **6.35**. Reaction of this ketone **6.35** in a mixture of ethanol and hydrazine monohydrate gave hydrazone **6.36** in 61% yield. The diazo compound of this hydrazone reacted smoothly with the thioketone **6.38** to give episulfide **6.39** in moderate yield. Desulfurization gave alkene **6.40**, which is ready for further functionalization.



Scheme 6.9 *A motor with functionalization in the upper half.*

6.3 Structural Analysis of the Dimethoxy Motor and Motor Functionalized Gold Colloids

6.3.1 X-ray Analysis and Determination of the Absolute Configuration

In order to demonstrate unequivocally the structure of the motor molecule **6.2** and to determine the preferred conformation of the stable isomer of **6.2**, it was decided to perform an X-ray crystallographic analysis. Furthermore, by using enantiomerically pure material the absolute configuration of the enantiomers can be determined. For this purpose, the racemic motor **6.2** consisting of two enantiomers, (2'*R*)-(*M*)-**6.2** and (2'*S*)-(*P*)-**6.2**, was resolved by preparative chiral HPLC using a Chiralcel AD column as the stationary phase and a mixture of heptane and *i*-propanol as the eluent in a ratio of 9:1. The first fraction was collected and recrystallized from methanol to yield single crystals suitable for X-ray analysis of **6.2**. This crystal was found to be monoclinic with space group $P2_1$. The asymmetric unit cell consisted of two molecules of **6.2**. The absolute configuration was determined to be (2'*R*)-(*M*)-**6.2** as is evident from Flack's refinement (**x**= 0.01(5)). This is the first example described in the literature in which the absolute configuration of a so-called second generation motor molecule has been determined other than by CD spectroscopy. The two residues, from hereon arbitrarily named residue 1 and 2, are identical, apart from minor distortions due to crystal packing effects. Relevant structural data for the X-ray crystallographic analysis are depicted in table 6.1 in the experimental section. The most important structural features of the molecule, depicted in figure 6.2, are the overall helical shape and the (pseudo-)axial orientation of the methyl substituent.

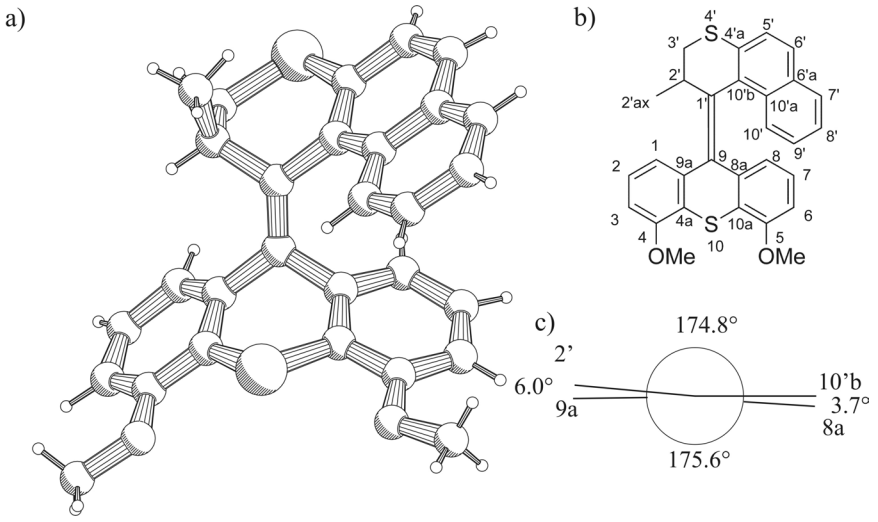


Figure 6.2 *Pluto drawings of (2'R)-(M)-**6.2** seen perpendicular to the central double bond (a), the numbering employed for the molecule (b) and the Newman projection (c).*

The (pseudo-)axial orientation of the methyl substituent is essential for the sterically overcrowded alkenes to perform a unidirectional rotation around the central double bond and to function as a molecular motor. The geometry of residue 1 of (2'*R*)-(*M*)-**6.2** in the solid state is characterized as follows: central double bond, $C_{1'}$-C_9 = 1.360 Å; bond angles around the central double bond, C_{8a}-C_9-C_{9a} = 112.4°, C_{9a}-C_9-$C_{1'}$ = 122.3°, C_{8a}-C_9-$C_{1'}$ = 125.2° (total angle around C_9 is 359.9°), $C_{10'b}$-$C_{1'}$-$C_{2'}$ = 113.0°, $C_{10'b}$-$C_{1'}$-C_9 = 124.7°, $C_{2'}$-$C_{1'}$-C_9 = 122.1° (total angle around $C_{1'}$ is 359.8°); the torsion angle between the naphthalene plane of the upper part and the central double bond, $C_{10'a}$-$C_{10'b}$-$C_{1'}$-C_9 = -54.6°; torsion angles at the central double bond, $C_{10'b}$-$C_{1'}$-C_9-C_{8a} = 3.7°, $C_{2'}$-$C_{1'}$-C_9-C_{9a} = -6.0°, C_{8a}-C_9-$C_{1'}$-$C_{2'}$ = 178.5°, C_{9a}-C_9-$C_{1'}$-$C_{10'b}$ = 179.2°. The helical structure of the molecule is especially evident from the torsion angles between the thioxanthene arene moieties of the lower part and the central double bond, $C_{1'}$-C_9-C_{9a}-C_1 = 57.9°, $C_{1'}$-C_9-C_{8a}-C_8 = -52.3° and the angle between the least square planes of both arenes: 44.7°. The geometry of residue 2 is characterized as follows: central double bond, $C_{1'}$-C_9 = 1.357 Å; bond angles around central double bond, C_{8a}-C_9-C_{9a} = 112.4°, C_{8a}-C_9-$C_{1'}$ = 123.3°, C_{9a}-C_9-$C_{1'}$ = 124.1° (total angle around C_9 is 359.8°), $C_{10'b}$-$C_{1'}$-$C_{2'}$ = 113.6°, $C_{10'b}$-$C_{1'}$-C_9 = 123.7°, $C_{2'}$-$C_{1'}$-C_9 = 122.6° (total angle around $C_{1'}$ is 359.9°); the dihedral angle between the naphthalene plane of the upper part and the central double bond, $C_{10'a}$-$C_{10'b}$-$C_{1'}$-C_9 = -48.5°; torsion angles at the central double bond, $C_{10'b}$-$C_{1'}$-C_9-C_{8a} = 4.6°, $C_{2'}$-$C_{1'}$-C_9-C_{9a} = -5.5°, C_{8a}-C_9-$C_{1'}$-$C_{2'}$ = -179.9°, C_{9a}-C_9-$C_{1'}$-$C_{10'b}$ = 179.0°; torsion angles between the thioxanthene arene moieties of the lower part and the central double bond, $C_{1'}$-C_9-C_{9a}-C_1 = 58.9°, $C_{1'}$-C_9-C_{8a}-C_8 = -51.8° and the angle between the least-square planes of both arenes: 44.0°. The methyl substituent clearly adopts a (pseudo-)axial orientation as can be seen from the torsion angle C_9-$C_{1'}$-$C_{2'}$-$C_{2'ax}$ which is 131.4° and 128.7° for residues 1 and 2, respectively. In both residues, the central double bond is only slightly twisted. Each sp^2 carbon of the central double bond, $C_{1'}$-C_9, remains essentially planar. The lower thioxanthene part of the molecule adopts a folded structure to diminish the steric strain around the central double bond and, together with the pseudo-boat conformation of the thiopyran ring of the upper part, is responsible for the helical shape of the entire molecule. X-ray analysis of colloids **6.1** is not possible. However, the motor moiety attached to the gold core is expected to have a similar structure compared to that of **6.2**, especially because of the close resemblance of the UV-Vis and the CD spectra of the two compounds (see below).

6.3.2 ^{1}H NMR and Two Dimensional ^{1}H NMR Spectroscopy

Although molecular motor **6.2** has been characterized by X-ray crystallography, detailed information of the proton absorptions in the ^{1}H NMR spectrum were needed in order to assign the proton absorptions of the deuterated analogue **6.57** (*vide infra*). Therefore, COSY, NOESY and ROESY experiments were performed. Already from the ^{1}H spectrum of **6.2** shown in figure 6.3, all individual signals can be distinguished and from the COSY spectrum all spin systems can be assigned. In the NOESY and ROESY experiments, the most important observations leading to the individual assingments of all proton signals were made.

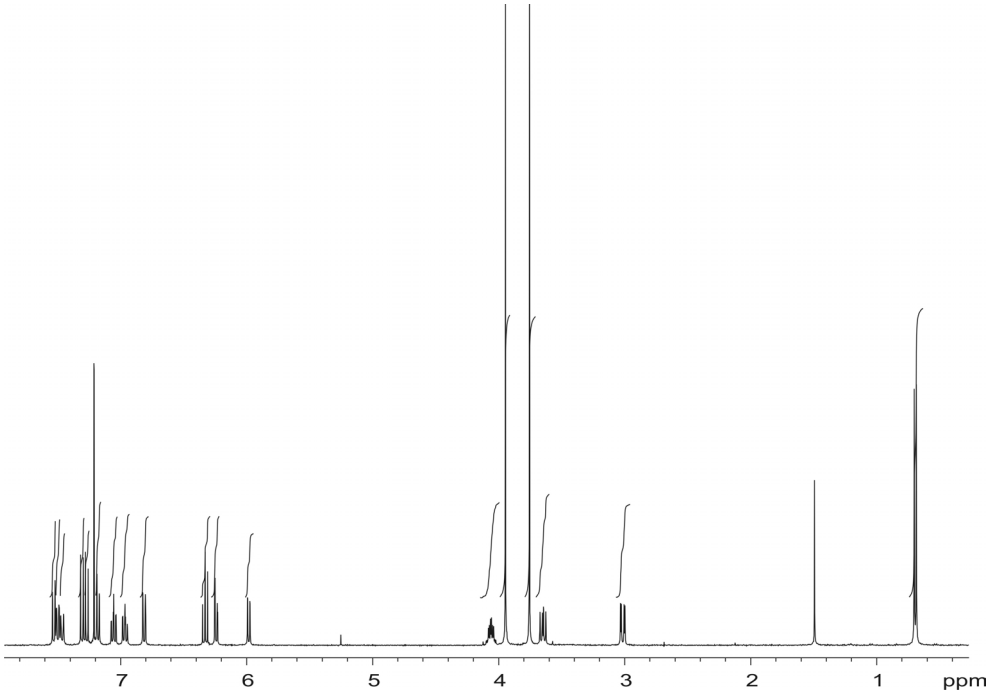


Figure 6.3 *^{1}H NMR spectrum of **6.2** taken at 400 MHz in $CDCl_3$.*

The signal of the methyl substituent, which was determined to be in a (pseudo-)axial orientation by X-ray crystallographic analysis, at δ 0.75 ppm has strong NOE interactions with the signals at δ 3.06 and 4.10 ppm. As was established by the COSY-experiment and the coupling constants in the ^{1}H NMR spectrum, the signal at δ 4.10 ppm belongs to the proton in the 2'-position ($H_{2'eq}$), which has an (pseudo-)equatorial conformation. The remaining two protons in the ring at the 3'-position have absorptions at δ 3.06 and 3.70 ppm. This takes into account the structure in the solid state, in which the distance between the $Me_{2'ax}$ and both protons at the 3'-position is smaller for the proton in the (pseudo-) equatorial orientation ($H_{3'eq}$) than for the proton in the (pseudo-)axial orientation ($H_{3'ax}$), a larger NOE interaction between $Me_{2'ax}$ and $H_{3'eq}$ is expected. The signal at δ 3.06 is therefore assigned to $H_{3'eq}$ and the signal at δ 3.70 to $H_{3'ax}$. The NOE-signal between the $Me_{2'ax}$ and $H_{3'ax}$ is significantly weaker and was only observed during the ROESY-experiment. This assignment is in agreement with the coupling constants between $H_{2'eq}$ and both $H_{3'}$-protons according to the Karplus equation. As is already evident from the X-ray structure, the distances between $H_{2'eq}$ and $H_{3'ax}$ in the upper half of the molecule and the proton at the 1-position (H_1) in the lower of the molecule are relatively small, 2.46 and 2.48 Å, respectively, due to the twisted nature of the molecule. Therefore, a clear NOE-signal is observed and the protons H_2 and H_3 can be assigned. Since the methoxy-signal at δ 4.00 shows a NOE-interaction with H_3, it can be concluded that it is located at the 4-position of the lower half. Similarly, the other methoxy signal at δ 3.81 exhibits an NOE-signal with an

aromatic proton at δ 6.30 ppm, which is therefore H_6. This is in agreement with the large upfield shift of protons H_6, H_7 and H_8 due to the ring current anisotropy enforced by the naphthalene moiety in the upper half. The ^{1}H NMR spectrum of the motor functionalized gold colloid **6.1** shows severe line broadening of all proton absorptions and no additional information could be obtained from the spectrum.

6.3.3 UV-Vis Spectroscopy

UV-Vis spectra in toluene for the functionalized gold nanoparticle **6.1** and the dimethoxy substituted motor molecule **6.2** are depicted in figure 6.4. All measurements were performed in toluene because the gold nanoparticles are not soluble in the usually employed *n*-hexane or dodecane.

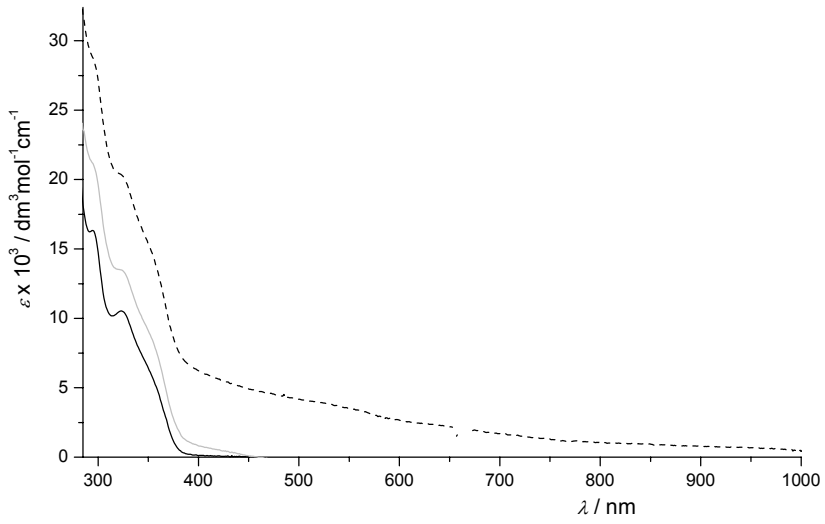


Figure 6.4 *UV-Vis spectra of methoxy-legged motor **6.2** (solid black), functionalized gold nanoparticles **6.1** (dashed black) in toluene (baseline: toluene) and the UV-Vis spectrum of functionalized gold nanoparticles **6.2** (solid grey) in toluene (baseline: octanethiol functionalized gold nanoparticles in toluene).*

The spectrum of **6.2** is characteristic for an overcrowded alkene and is similar to that of previously reported compounds.[3] The UV-Vis spectrum of the functionalized gold nanoparticles **6.1**, using the molar concentration of chromophores (sterically overcrowded alkenes) as determined by CD spectroscopy (see below) is an approximate superposition of the spectral bands of the alkene core and the broad band reaching far into the visible region, characteristic for gold nanoparticles. The absorption in the visible region of the spectrum is attributed to the surface plasmon absorption of the gold colloids. Due to the relatively small size of the nanoparticles, diameter approximately 2.4 nm, this absorption is significantly

broadened and dampened compared to larger systems.[16] The fact that the UV-Vis spectrum of the gold nanoparticles is indeed an approximate superposition can be illustrated by substraction of a baseline of gold colloid covered with octanethiol. The UV-Vis spectrum (figure 6.4) is almost identical to the UV-Vis spectrum of the dimethoxy motor **6.2** in solution, except for the discrepancy in the intensity, which can be attributed to the differences between the different gold nanoparticles in *e.g.* average size or size distribution. This indicates the absence of direct interaction of the chromophores with the gold core due to the eight carbon alkyl spacer, a requirement for the functioning of the molecular motor on a surface.

6.3.4 CD Spectroscopy

CD spectra in toluene of the dimethoxy substituted molecular motor **6.2** and the motor functionalized gold nanoparticles **6.1** are depicted in figure 6.5. When the CD spectrum of motor functionalized gold nanoparticles **6.1** is adjusted for the concentration of the chromophores, the CD spectra of **6.1** and **6.2** are almost identical. Unlike the UV-Vis spectra, where the gold core has a substantial influence, here only the chiral entity determines the CD absorptions. Again, there is no sign of direct electronic interaction of the chromophores with the gold core. The information that can be obtained from these spectra is limited by the cut-off wavelength of toluene (285 nm), therefore the CD spectrum of the free dimethoxy substituted motor **6.2** was also recorded in *n*-dodecane. The spectra in toluene and dodecane are comparable and also comparable to the spectra of other sterically overcrowded alkenes (figure 6.5). By comparison of the CD spectra with the spectra of previously studied sterically overcrowded alkenes, the configuration of the motor can be assigned to be (*M*). The assignment by CD of the absolute configuration is in complete agreement with the determination of the absolute configuration by X-ray crystallography (see above).

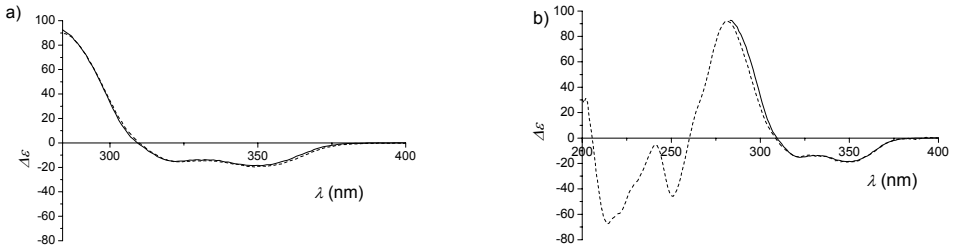


Figure 6.5 *Depicted on the left (a): CD spectra of dimethoxy substituted motor **6.2** (solid line) and the functionalized gold nanoparticle (dashed line) in toluene; depicted on the right (b): CD spectra of dimethoxy substituted motor **6.2** in toluene (solid line) and n-dodecane (dashed line).*

From X-ray analysis (see above) and for other motor systems, it is known that there is an energetic preference for the methyl substituent to adopt a (pseudo-)axial orientation. This prefered orientation of the methyl substituent to adopt a (pseudo-)axial orientation results in

an exclusive presence of the (2'*R*)-(*M*) conformational isomer of both (2'*R*)-**6.1** and (2'*R*)-**6.2** under thermal equilibrium conditions. The isomer used for all experiments for both the free dimethoxy-legged motor **6.2** and the motor anchored to gold **6.1** can therefore be assigned as (2'*R*)-(*M*).

Comparison of the UV-Vis spectrum and especially the CD spectrum of a toluene solution of the gold colloids **6.1** with the molar spectroscopic data obtained for the dimethoxy substituted parent compound **6.2** gives the molar quantity of chromophoric alkenes per gram of nanoparticle. Together with the known particle size (TEM: d= 2.11 nm) and the density of gold (19.3 g cm^{-3})[17] the number of alkenes per nanoparticle can be calculated to be about 30. Since a 2.11 nm core diameter corresponds to 289 gold atoms the overall formula of monolayer protected gold cluster is $Au_{289}((S(CH_2)_8O)_2C_{27}H_{18}S_2)_{30}$.

6.3.5 FT-IR Spectroscopy

FT-IR spectroscopy was used to confirm the attachment of the molecular motor onto the gold colloid by measuring the vibrational spectrum in the solid state in KBr. The vibrational spectra measured in reflection mode of the free motor **6.2** and the motor capped on gold **6.1** show distinct differences but comparison of both spectra clearly indicates the presence of the alkene structure on the gold nanoparticle (figure 6.6). The fingerprint area (500-2000 cm^{-1}) of the IR absorption spectrum is dramatically changed for the nanoparticles **6.1** relative to the free methoxy-legged motor **6.2**. This indicates a substantial change in the local environment of the individual overcrowded alkene chromophores, indicating either substantial intramolecular interaction between different chromophoric moieties (*e.g.* π–π interaction) on one gold particle, which is not surprising taking into consideration that there is only approximately 0.46 nm^2 surface area per alkene molecule. This corresponds to 0.23 nm^2 surface area per linked sulfur atom, which is in accordance with early electron diffraction studies on monolayers of alkanethiolates on flat gold-surfaces where the area per thiol molecule was calculated to be 0.214 nm^2.[18] The small increase in the surface area per thiol group for the nanoparticles can be attributed to the curvature of the surface. A second reason for the changes in the fingerprint region can be a direct interaction between the chromophoric moieties and the gold surface which is less likely considering the close packing of the chromophores as just described and the relatively long C_8-spacer used. The absence of direct interaction between gold and the chromophoric olefinic moieties is further supported by UV-Vis and CD spectroscopic data (see above and below).

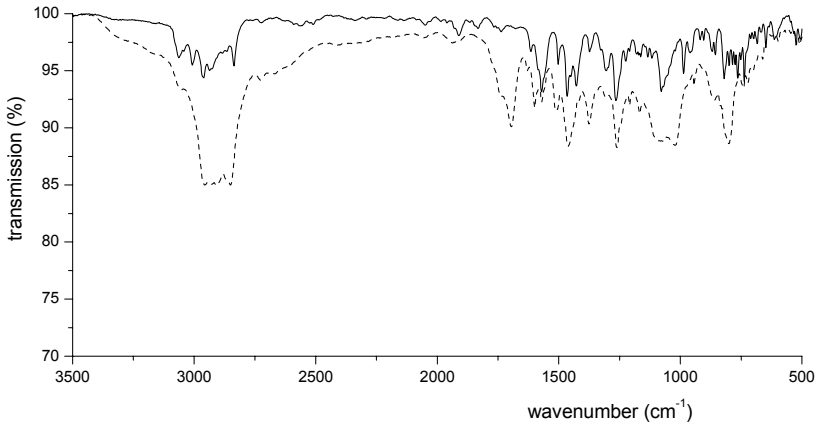


Figure 6.6 *FT-IR of methoxy-legged motor* ***6.2*** *(solid) and functionalized gold nanoparticles* ***6.1*** *(dashed) (KBr).*

6.3.6 Dynamic Light Scattering

In order to determine the size of the functionalized gold colloid, dynamic light scattering (DLS) measurements were performed at 30.0ºC at a wavelength (λ_0) of 633.3 nm. For the measurements a solution containing 3.1 mg of nanoparticles in 1 ml of toluene was used. Prior to measurement, the samples were centrifuged for 5 min at 3000 rpm to remove any interfering dust particles from the scattering volume. The intensity autocorrelation functions obtained from the DLS were analyzed using CONTIN.[19] The intensity mean particle size or dynamic diameter was determined to be 2.8 nm with a Gaussian-like distribution ranging from 1.6 to 5.7 nm.

6.3.7 Transmission Electron Microscopy

The size of the gold nanoparticles capped by the dilegged motor molecular motor **6.1** was examined by transmission electron microscopy (TEM). A typical TEM image (left) and particle size distribution diagram (right) are shown in figure 6.7. The particles are well dispersed and spherical in shape. The average gold core diameter of the particles is 2.11 nm with a distribution range of 1.5 to 4.0 nm. This core diameter corresponds to an average of 289 gold atoms per colloid. These results are in accordance with the results from the dynamic light scattering measurement, which indicated the diameter of the total colloid rather than only the gold core and, as a consequence, using DLS a larger particle diameter was found.

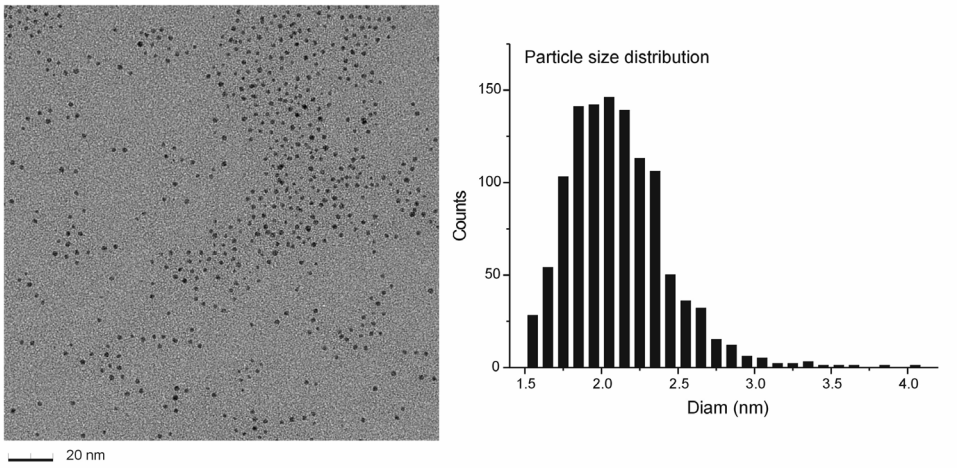
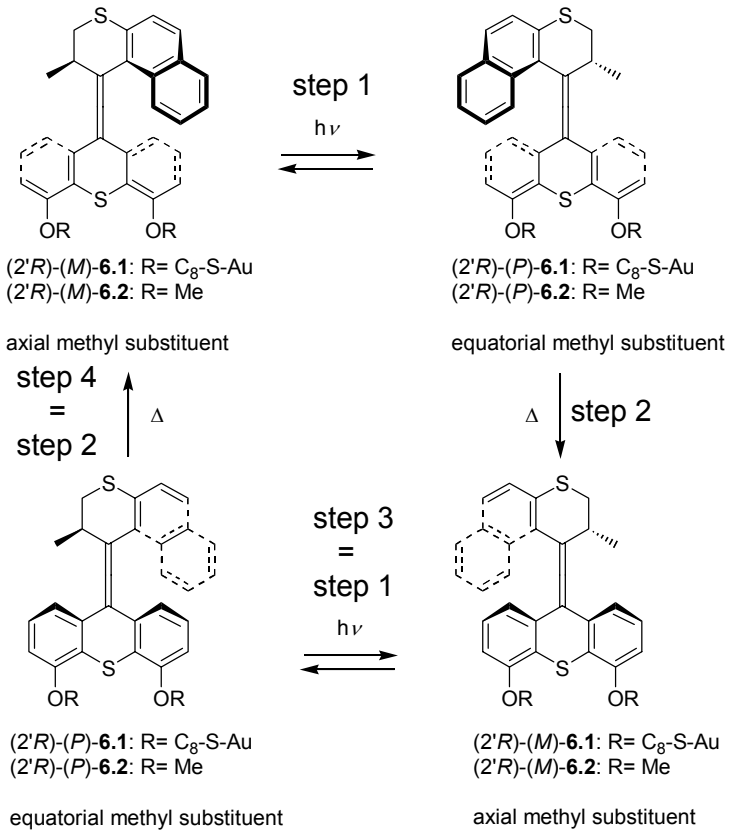


Figure 6.7 *TEM image (left) and particle size distribution graph (right) of capped gold nanoparticles* ***6.1****.*

6.4 Unidirectional Rotation of Functionalized Gold Colloids

Based on our experience with similar overcrowded alkenes, it was expected that the alkene **6.2** and the functionalized nanoparticles **6.1** would function as light-driven unidirectional molecular motors as depicted in scheme 6.10. Two energetically uphill photochemical isomerization steps each followed by a subsequent energetically downhill unidirectional thermal helix inversion should add up to a full 360º rotation of one half of the molecule with respect to the other. The direction of rotation is fully controlled by the configuration of the stereogenic center. Starting either from (2'*R*)-(*M*)-**6.1** or (2'*R*)-(*M*)-**6.2**, upon photoirradiation a *cis-trans* isomerization should occur which inverts the helicity of the molecule. As a consequence of this process, the methyl substituent is forced to adopt the energetically disfavored (pseudo-)equatorial orientation resulting in the respective (2'*R*)-(*P*) conformational isomers. Due to the two bridging sulfur atoms in both upper and lower half, the isomers with an equatorial methyl substituent are expected to be relatively stable at room temperature. Upon thermal treatment, however, these isomers should undergo a helix inversion resulting in the formation of the initial (2'*R*)-(*M*) isomer again after an, in total, 180º rotation of the *rotor* upper half of the molecule in a counterclockwise fashion with respect to the *stator* lower half. Another completely identical photoisomerization step followed by thermal helix inversion should then result in a full unidirectional 360º rotation of the *rotor* half. The unidirectionality of the rotary process is ensured by the irreversibility of the energetically downhill thermal helix inversion steps. In case of the nanoparticles this scheme should apply for all the motor entities attached to the surface. It should be noted that for theses types of alkenes with a symmetric lower *stator* half, for the (2'*R*)-isomer only two conformations make up the four-state rotational cycle. After two steps, one photoisomerization step and one thermal helix inversion, the motor part of the molecule

returns to its initial stable state. The anticipated rotational cycle as depicted below was tested for both systems **6.1** and **6.2**.



Scheme 6.10 *The anticipated four-state unidirectional rotation for compounds **6.1** and **6.2**.*

6.4.1 Rotary experiments followed by ^{1}H NMR

The ^{1}H NMR experiments to prove the rotary cycle for the dimethoxy substituted **6.2** were performed in toluene-d_8. Toluene was chosen in order to have conditions identical to those to be used in the UV-Vis and CD experiments. In the ^{1}H NMR spectrum recorded in toluene-d_8 indicative signals of stable (2'R^*)-(M^*)-**6.2** are the doublet of the methyl in the upper half at δ 0.5 ppm, the signals of both methoxy substituents of the lower half at δ 3.2 and 3.4 ppm and an absorption of an aromatic proton at relatively low field at δ 7.9 ppm. The examination of the rotary process was started with the irradiation of racemic (2'R^*)-(M^*)-**6.2** with polychromatic light ($\lambda \geq$ 280 nm, T= 0°C). In order to determine the photostationary state (PSS), ^{1}H NMR spectra were recorded in time. When no further change was observed, the PSS had been reached. The irradiation of the stable (2'R^*)-(M^*)-**6.2** results in the formation of the unstable (2'R^*)-(P^*)-**6.2,** in which the methyl substituent

changes its orientation from (pseudo-)axial to (pseudo-)equatorial. This was concluded from the shifts observed in the ^{1}H NMR spectrum. The indicative absorption of the methyl substituent in the upper half for formation of an equatorial, unstable isomer, was shifted from δ 0.5 ppm to δ 0.9 ppm. This shift occurs due to the increased shielding of the (pseudo-)equatorial methyl substituent in (2'R^*)-(P^*)-**6.2** by the neighboring lower half arene moiety. Furthermore, the absorptions of the three other protons in the upper ring move to higher field. The signals for the methoxy substituents are only slightly shifted upfield and overlap with the proton absorptions of the thiopyran upper half of the molecule. Most aromatic signals strongly overlap and there is only one apparent absorption which was shifted from δ 7.9 ppm to δ 7.6 ppm. By integration of the various signals, the ratio of stable (2'R^*)-(M^*)-**6.2** and unstable (2'R^*)-(P^*)-**6.2** at the PSS was determined to be 9:91. This ratio between stable (2'R^*)-(M^*)-**6.2** and unstable (2'R^*)-(P^*)-**6.2** at the PSS could be further improved to 6 : 94, by irradiation with monochromatic light (λ= 365 nm, T= 0°C).

6.4.2 Photochemical Behavior of the Dimethoxy Substituted Motor

A 1.688 x 10^{-5} M solution of (2'*R*)-(*M*)-**6.2** in toluene was irradiated with polychromatic light (T= 0°C, $\lambda \geq$ 280 nm) and the changes in the UV-Vis and CD spectra were monitored in time until no further change occurred, indicating that the photostationary state ($PSS_{\geq 280\ nm}$) was reached (figure 6.8a and 6.8b). The major signal in the CD spectrum changed from positive ($\Delta\varepsilon$ +92.6 (λ = 283 nm)) to negative ($\Delta\varepsilon$ -43.9 (λ = 283 nm)) indicative of the change in helicity going from (2'*R*)-(*M*)-**6.2** to (2'*R*)-(*P*)-**6.2**. In the UV-Vis spectrum a decrease in the intensity of the high wavelength band (from ε 6400 (λ =350 nm) to ε 4300 (λ =347 nm)) was most indicative for the formation of (2'*R*)-(*P*)-**6.2**. The clear isosbestic point(s) in both the CD ($\lambda\approx$ 305 nm) and the UV-Vis spectra (λ= 291, 299, 305, 321 nm) indicate a clean photochemical conversion from (2'*R*)-(*M*)-**6.2** to (2'*R*)-(*P*)-**6.2** (scheme 6.8). From the data obtained by UV-Vis and CD spectroscopy and the ratio (9:91) in the PSS as determined by ^{1}H NMR, the UV-Vis and CD spectra for the pure unstable (2'*R*)-(*P*)-**6.2** were calculated as depicted in figure 6.8. Unfortunately, this unstable (2'*R*)-(*P*)-**6.2** could not be obtained in pure form via chromatographic separation.

The photostationary state ratio is governed by the ratio of extinction coefficients of the two forms of a photochromic system. From the ratio of the UV-Vis spectra of (2'*R*)-(*M*)-**6.2** and (2'*R*)-(*P*)-**6.2**, the ideal wavelength for formation isomer (2'*R*)-(*P*)-**6.2** is 365 nm. Subsequent irradiation at this wavelength of the sample (Mercury line filter 365 nm (typical bandwidth 10 nm)) indeed resulted in a more selective isomerization with a photostationary state ($PSS_{365\ nm}$) consisting of 94% (2'*R*)-(*P*)-**6.2** and 6% of (2'*R*)-(*M*)-**6.2** (as was determined by ^{1}H NMR) with concomittant further increase of the major CD band at 283 nm ($\Delta\varepsilon$= -59.6) and decrease of the intensity of the high wavelength band at 347 nm (ε= 4000).

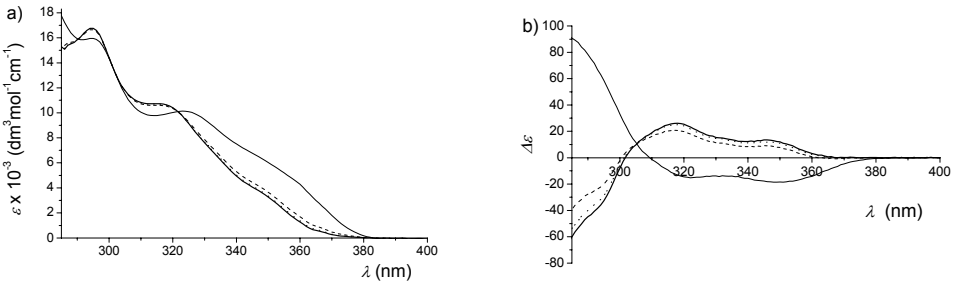


Figure 6.8 *a) Depicted on the left (a): UV-Vis spectra of pure (2'R)-(M)-**6.2** (solid line), $PSS_{\geq 280\ nm}$ (dashed line), $PSS_{365\ nm}$ (dotted line) and the calculated UV/Vis spectrum of (2'R)-(P)-**6.2** (thick solid line, see text for details) recorded in toluene; b) depicted on the right CD spectra of pure (2'R)-(M)-**6.2** (solid black), $PSS_{\geq 280\ nm}$ (dashed black), $PSS_{365\ nm}$ (dotted black) and the calculated CD spectrum of (2'R)-(P)-**6.2** (thick solid, see section 6.4.2 for details) recorded in toluene.*

6.4.3 Thermal Behavior of the Dimethoxy Substituted Motor

Heating this photostationary state sample to a temperature higher than 50ºC resulted in a full conversion of all (2'*R*)-(*P*)-**6.2** present to stable (2'*R*)-(*M*)-**6.2**, as a result of the anticipated thermal helix inversion (step 2 in scheme 6.10). UV-Vis, CD and ^{1}H NMR data are all consistent with this observation. The kinetics of this thermal helix inversion were examined by CD spectroscopy by monitoring the change in CD intensity at a certain temperature in time (figure 6.9). From the change in CD monitored in time at various temperatures (T= 50, 60, 70, 80ºC), the rate constant (k_t) was determined and subsequently used to calculated Gibbs energy of activation ($\Delta^{\ddagger}G^{\theta}$ = 94±1 kJ·mol^{-1}), enthalpy of activation ($\Delta^{\ddagger}H^{\theta}$ = 27.2±0.2 kJ·mol^{-1}), and the entropy of activation ($\Delta^{\ddagger}S^{\theta}$ = -227±4 kJ·mol^{-1}), using the Eyring equation. This corresponds to a half-life of 5614 s at room temperature (293.15 K) for the thermal helix inversion of (2'*R*)-(*P*)-**6.2** to (2'*R*)-(*M*)-**6.2**.

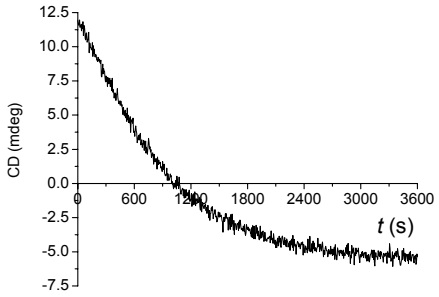


Figure 6.9 *Kinetics of the thermal helix inversion from (2'R)-(P)-**6.2** (PSS) to (2'R)-(M)-**6.2**: CD signal at 316 nm monitored in time at 80ºC in toluene solution.*

These two steps, photoinduced *cis-trans* isomerization followed by unidirectional thermal helix inversion result in a 180º rotation of the *rotor* half of the molecular in a counterclockwise fashion with respect to the *stator* half of the molecule. The net result of this semi rotation is the formation of the initial (2'*R*)-(*M*)-**6.2** again. The exact same two-step process can be performed again, extending the rotary motion to a full 360º unidirectional rotation. Under the condition of continuous irradiation at elevated temperature this molecule will perform a continuous unidirectional rotation around the central olefinic bond, which functions as the axis of rotation. This sterically overcrowded alkene thus functions as a light-driven molecular motor in full accordance with previously developed systems. That no other processes occur during irradiation and thermal isomerization will be demonstrated later in this chapter with a deuterated analogue of the molecular motor **6.2**.

6.4.4 Photochemical Behavior of the Motor Functionalized Gold Nanoparticles

Analogous to the experiments performed for parent compound **6.2**, the photochemical and thermal properties of the motor functionalized nanoparticles **6.1** were studied in toluene solution. Using the same conditions as employed for the photochemical experiments on compound **6.2**, a 1.035 x 10^{-5} M solution (chromophore concentration) in toluene was irradiated at $\lambda \geq 280$ nm.

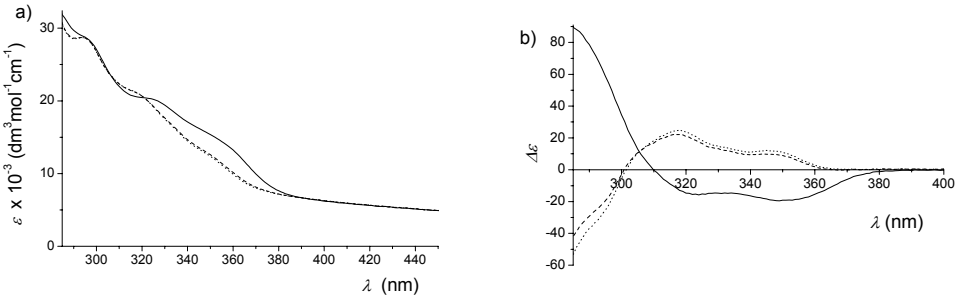


Figure 6.10 *a) Depicted on the left: UV-Vis spectra of pure (2'R)-(M)-**6.1** (solid), $PSS_{\geq 280\ nm}$ (dashed), and $PSS_{365\ nm}$ (dotted) in toluene; all spectra are adjusted for molar concentration of chromophores; b) depicted on the right: CD spectra of pure (2'R)-(M)-**6.1** (solid), $PSS_{\geq 280\ nm}$ (dashed), and $PSS_{365\ nm}$ (dotted) in toluene; all spectra are adjusted for molar concentration of chromophores.*

The UV-Vis and CD spectra of (2'*R*)-(*M*)-**6.1** before irradiation (solid black) and the $\lambda \geq 280$ nm photostationary state ($PSS_{\geq 280\ nm}$; dashed black line) are depicted in figure 6.10a and 6.10b, respectively. Analogously to compound **6.2**, the major CD signal changed from positive ($\Delta\varepsilon$ +91.0 ($\lambda = 283$ nm)) to negative ($\Delta\varepsilon$ -46.4 ($\lambda = 283$ nm)) signal. This inversion of the sign is indicative of the inversion of helicity going from (2'*R*)-(*M*)-**6.1** to (2'*R*)-(*P*)-**6.1**. In the UV-Vis spectrum a decrease in the intensity of the high wavelength band (from ε 15188 ($\lambda = 351$) to 12375 ($\lambda = 351$ nm)) was most indicative for the formation of (2'*R*)-

(*P*)-**6.1**. The clear isosbestic point(s) in both the CD ($\lambda \approx 305$ nm) and the UV-Vis spectra ($\lambda = 307, 321$ nm) again indicate a clean photochemical conversion from (2'*R*)-(*M*)-**6.1** to (2'*R*)-(*P*)-**6.1**. As for compound **6.2,** subsequent irradiation at a more appropriate 365 nm wavelength resulted in more selective formation of (2'*R*)-(*P*)-**6.2** with concomittant changes in both UV-Vis and CD spectra (figures 6.10a and 6.10b).

It is impossible to assess unequivocally the photostationary state ratios for the sterically overcrowded alkene functionalized gold nanoparticles **6.1** after either $\lambda \geq 280$ nm or $\lambda = 365$ nm irradiation. Common methods like HPLC and ^{1}H NMR (employed for the dimethoxy substituted parent compound **6.2**) are not suitable here and CD spectroscopy can only be employed for this purpose when the CD of both states of the bistable system are known. Nevertheless, the selectivity of the photochemical interconversion can be estimated by comparison of the CD spectra of the photostationary states of the nanoparticles with those of the dimethoxy substituted molecular motor **6.2**, where the PSS ratios were separately determined by ^{1}H NMR. Examination of the CD spectra (figure 6.8b and 6.10b) shows increased absorption bands in the CD spectrum of the ≥ 280 nm photostationary state of the nanoparticle solution (*e.g.* $\Delta\varepsilon$ +22.2 ($\lambda = 317$ nm) for **6.1** vs. 20.7 ($\lambda = 317$ nm) for **6.2**) but slightly decreased absorption bands in the CD spectrum of the 365 nm photostationary state (*e.g.* $\Delta\varepsilon$ +24.7 ($\lambda = 318$ nm) for **6.1** vs. 25.0 ($\lambda = 318$ nm) for **6.2**). These data most probably indicate that the photoisomerization step for the motor mounted on a gold nanoparticle is more selective in case of $\lambda \geq 280$ nm irradiation and slightly less selective in case of $\lambda = 365$ nm irradiation, although some influence of the different environments of the chromophores on the CD spectra of both the stable and unstable form of **6.1** cannot be excluded. Nevertheless, it can be concluded that the selectivities of the photoisomerization of the sterically overcrowded alkenes are only slightly influenced by the constraints enforced by the attachment to a gold nanoparticle.

The comparable efficiency of the photoisomerization steps of the bare dimethoxy substituted motor **6.2** and the motor nanoparticles capped onto colloidal gold **6.1** indicate that the chromophores on the nanoparticles are not very densely packed. For comparison, azobenzene self-assembled monolayers on a gold surface are hardly photoactive due to dense packing of the photochromic moiety.[10] It is known that aggregation between photoactive compounds is weaker on colloidal gold compared to planar gold surfaces because the curved surface of the colloid gives the mounted chromophores an increased free volume for their photochemical reaction.[20]

6.4.5 Thermal Behavior of the Motor Functionalized Gold Nanoparticles

Also for **6.1**, heating of the photostationary state sample to a temperature higher than 50ºC resulted in a full conversion of all (2'*R*)-(*P*)-**6.1** present to stable (2'*R*)-(*M*)-**6.1**, as a result of the anticipated thermal helix inversion (step 2 in scheme 4). UV-Vis and CD data are consistent with this observation. The kinetics of this thermal helix inversion were examined by CD spectroscopy monitoring the change in CD intensity at a certain temperature in time (figure 6.11). From the change in CD monitored in time at various temperatures ($T = 50$, 60, 70, 80ºC), the rate constant (k_t) was determined and subsequently used to calculate

Gibbs energy of activation ($\Delta^{\ddagger}G^{\theta}$ = 96±3 kJ·mol^{-1}), the enthalpy of activation ($\Delta^{\ddagger}H^{\theta}$ = 37±1 kJ·mol^{-1}), and the entropy of activation ($\Delta^{\ddagger}S^{\theta}$ = -200±4 kJ·mol^{-1}), using the Eyring equation. This corresponds to a half-life of 11896 s at room temperature (293.15 K) for the (2'*R*)-(*P*)-**6.1** to (2'*R*)-(*M*)-**6.1** interconversion. This energy barrier is slightly higher than the barrier found for **6.2** and results in an approximate doubling of the half-life for thermal helix inversion at room temperature. This can most likely be attributed to the restricted flexibility of the sterically overcrowded alkene when mounted onto a gold surface. At elevated temperatures this effect becomes less pronounced: at 80ºC the half-lives of the thermal helix inversion are similar: 704 s and 725 s for **6.2** and **6.1**, respectively.

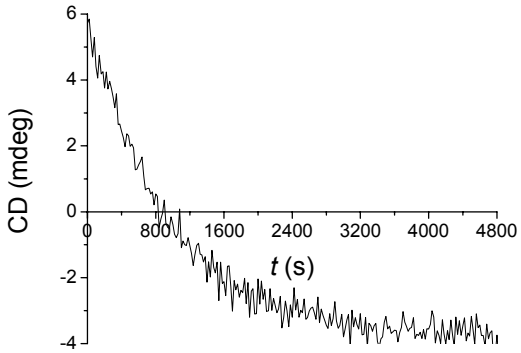


Figure 6.11 *Kinetics of the thermal helix inversion from (2'R)-(P)-**6.1** (PSS) to (2'R)-(M)-**6.1**: CD signal at 317 nm monitored in time at 80ºC in toluene solution.*

Completely analogous to compound **6.2**, these two steps, photoinduced *cis-trans* isomerization followed by unidirectional thermal helix inversion, result in a 180º rotation of the rotor half of the molecule in a counterclockwise fashion with respect to the stator half of the molecule and the net result of this semi rotation is the formation of the initial (*2'R*)-(*M*)-**6.1** again. The exact same two-step process can be performed again, extending the rotary motion to a full 360º unidirectional rotation. Under irradiation at elevated temperature this molecule will perform a continuous unidirectional rotation around the central olefinic bond, which functions as the axis of rotation. It was shown that the molecular motor on a gold nanoparticle functions in the same way as a molecular motors in solution. Light-driven unidirectional rotary motion is possible for a molecular motor fixed to a gold nanoparticle, which is a highly promising result in view of alternative surface attachments and development of molecular motors onto gold surfaces.

6.4.6 Controlling the Attachment of the Motor on the Gold Surface

In order to prove fully that what is measured here (the sterically overcrowded alkene attached to a gold surface performing unidirectional rotation) is not merely a matter of the alkene being detached in solution (cleavage of the sulfur-gold bond) and then undergoing either photochemical isomerization (step 1) under irradiation or thermal helix inversion

(step 2) upon heating followed subsequently by reattachment of the alkene (reformation of the sulfur-gold bond), we performed two tests.

First, a highly concentrated solution of nanoparticles **6.1** in toluene was irradiated with $\lambda \geq$ 280 nm, completely analogous to the experiments described above monitoring the photoisomerization by UV-Vis spectroscopy (1 mm cell). During the final stage of the irradiation the solution was quickly added to an approximate ten-fold excess of methanol. The precipitated gold nanoparticles were redissolved in toluene and both this solution and the mother liquid were investigated by UV-Vis spectroscopy. This procedure was repeated after sequential heating of the toluene solution at 80ºC for two hours, allowing full thermal helix inversion. In both cases the nanoparticle solution before and after precipitation showed the same UV-Vis characteristics, although due to both precipitation steps some dilution occurred. The methanol-toluene mother liquor in both cases did not have any substantial UV-Vis absorption. This indicated that the molecular motor is neither detached from the solution in the photochemical nor in the thermal step of the rotation cycle (the "free" molecular motor in whatever form (dithiol or disulfide) is expected to be soluble in methanol, at least to some extent, as the formation of the dithiol (see above) is performed in a methanol-THF mixture).

As a second test, irradiation and subsequent heating was performed in the solid state. First, a solid racemic ((2'*R*)-(*M*) and (2'*S*)-(*P*)) sample of energetically stable compound **6.2** (as a thin film on glass prepared by evaporation of a drop of concentrated dichloromethane solution under ambient conditions) was irradiated for 4 h. UV-Vis examination before and after irradiation showed that the photoisomerization to form the unstable isomers indeed took place and with a selectivity comparable to the solution experiments. Subsequent heating (of a separate sample) resulted in full reversal to the initial stable isomers indicating that this molecular motor can function in the solid state similarly as in solution. For motor functionalized gold nanoparticles **6.1** a similar experiment was performed and also here photoisomerization took place in the solid state but was less efficient. Irradiation overnight (16h) resulted in only a small extent of photoisomerization compared to solution experiments. As was demonstrated by UV-Vis analysis, in only about 50 % of the chromophores photoisomerization had occured. This lower efficiency is probably due to the high extinction coefficient of the intensely black gold nanoparticles in the solid state. Nevertheless, these gold nanoparticles were after photoisomerization also submitted to heating and the chromophoric moieties completely reverted to their stable states as was demonstrated by UV-Vis measurements. These results prove that the unidirectional rotation for the molecular motors, both free and mounted to a gold nanoparticle, is feasible in the solid state.

6.5 A Deuterated Molecular Motor

Despite all experiments that can be performed with **6.1** and **6.2**, none would be conclusive if the molecular motor **6.2** or the legged-motor mounted on colloid **6.1**, can perform a unidirectional 360° rotation. Although it is assumed that **6.1** and **6.2** rotate in a satisfactory manner, from the performed experiments no definitive conclusion can be drawn since both

the molecules **6.1** and **6.2** possess a symmetric lower part. However, it is rather difficult to make any change in the lower half without effecting the properties of the molecule. Introduction of any substituent resulting in a dissymmetric lower half would allow direct observation of the rotary process by ^{1}H NMR. On the other hand, introduction of a substituent also results in different photochemical properties and increasing steric hindrance around the central double bond. From a more practical point of view, any separation of a *cis*- and *trans*-isomer is performed by chiral HPLC and therefore a motor molecule which can be separated by either column chromatography or recrystallization is preferred. Combining all these demands, a motor molecule was designed which is nearly identical to **6.2**, but on one of the methoxy subsituents the protons have been replaced by deuterons (figure 6.12). A requirement for this molecule to be successfully employed is that an intermediate compound can be separated into its *cis*- and *trans*-isomers.

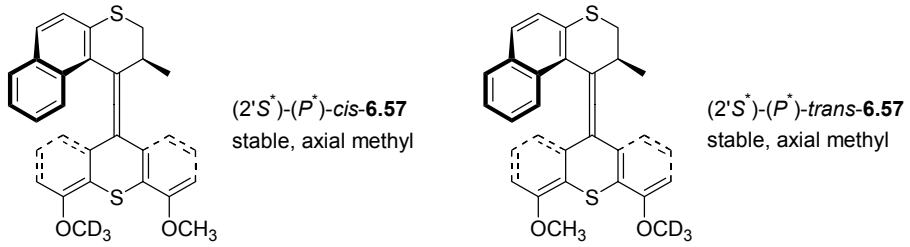
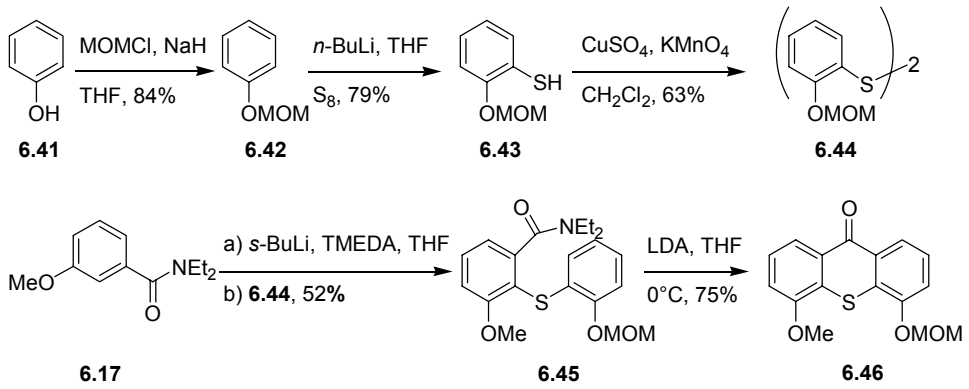


Figure 6.12 *Deuterated molecular motors (2'S*)-(P*)-cis-**6.57** and (2'S*)-(P*)-trans-**6.57***

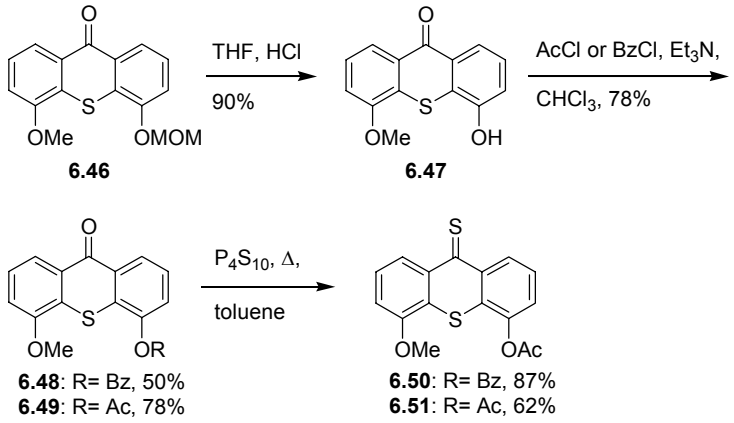
6.5.1 Synthesis of the Deuterated Motor

The synthesis of motor **6.57** features the same synthetic methodology as was used for **6.2**. A difference is the use of a protecting group in the synthesis at the position where a deuterated methoxy group will be introduced. In the first step, phenol **6.41** was protected with a methoxymethyl group to provide after reaction **6.42** by deprotonation with NaH and subsequent reaction with MOMCl. The methoxymethyl group is an excellent ortho-directing group for metallation of the arene moiety and by reaction with *n*-BuLi in THF followed by reaction with elemental sulfur the thiol **6.43** was obtained. The thiol was converted to the disulfide **6.44** by using $CuSO_4/KMnO_4$ in CH_2Cl_2. This disulfide was allowed to react with the lithiated species **6.18** prepared from **6.17** using *s*-BuLi and TMEDA in THF, as described above, to provide **6.45**. The desired amide **6.45** was then converted by an anionic Friedel-Crafts reaction to ketone **6.46**.



Scheme 6.11 *Synthesis of the MOM protected lower half ketone **6.46**.*

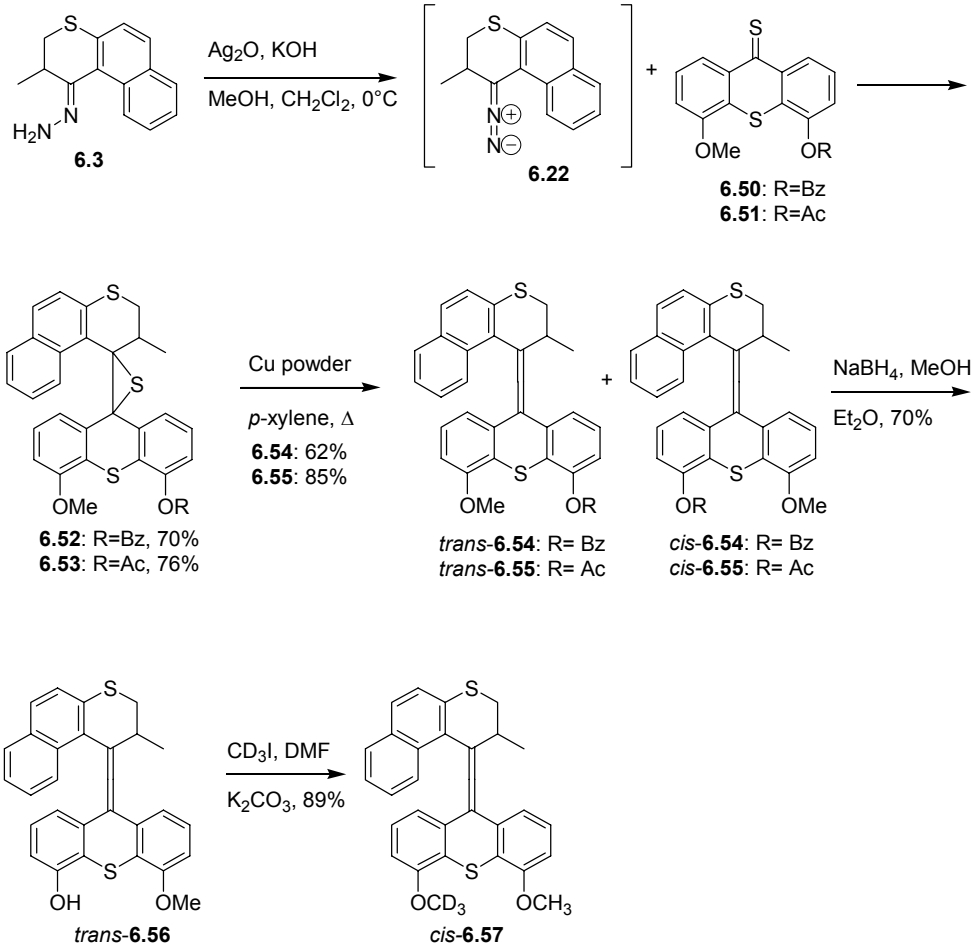
The MOM group, which is not only a protecting group but also was necessary for the *ortho*-lithiation of the phenol, has to be cleaved off since it does not tolerate the reaction with P_4S_{10}. The phenol **6.47**, obtained by cleavage of the MOM-group of **6.46** by HCl was therefore converted to both the benzoyl and acetyl protected compounds **6.48** and **6.49**. The conversion to the acetyl protected **6.49** proceeded more readily then the benzoyl protected **6.48**. More important is that both benzoyl and acetyl groups have proven to be stable under the conditions used for conversion of the the ketone to the thioketone moieties in **6.50** and **6.51**. The yield of the benzoyl protected thioketone **6.50** was slightly higher with 87% yield. Both thioketones **6.50** and **6.51** are slightly unstable and slowly degrade.



Scheme 6.12 *Synthesis of the thioketones **6.50** and **6.51**.*

Both thioketone **6.50** and **6.51** were directly used in the Barton-Kellogg reaction with hydrazone **6.3**. In both cases this reaction yielded a mixture of two stereoisomeric episulfides **6.52** and **6.53** in approximately equal amounts in 70% and 76% yield, respectively. No efforts were made to separate the episulfides into the individual isomers, but the synthesis was continued to give alkenes **6.54** and **6.55** as a mixture of *cis*- and

trans-isomers after desulfurization with triphenylphosphine. Remarkable is the difficult desulfurization of **6.52**, which proceeded only after heating at reflux for prolonged reaction times. The *cis*- and *trans*-isomers of **6.54** could only be separated using chiral HPLC using an OD column as the stationary phase and a mixture of heptane and *i*-propanol in a ratio of 98:2 as the eluent. The amount of material obtained was too small to conduct further experiments.



Scheme 6.13 *Synthesis of deuterated molecular motor **6.57**.*

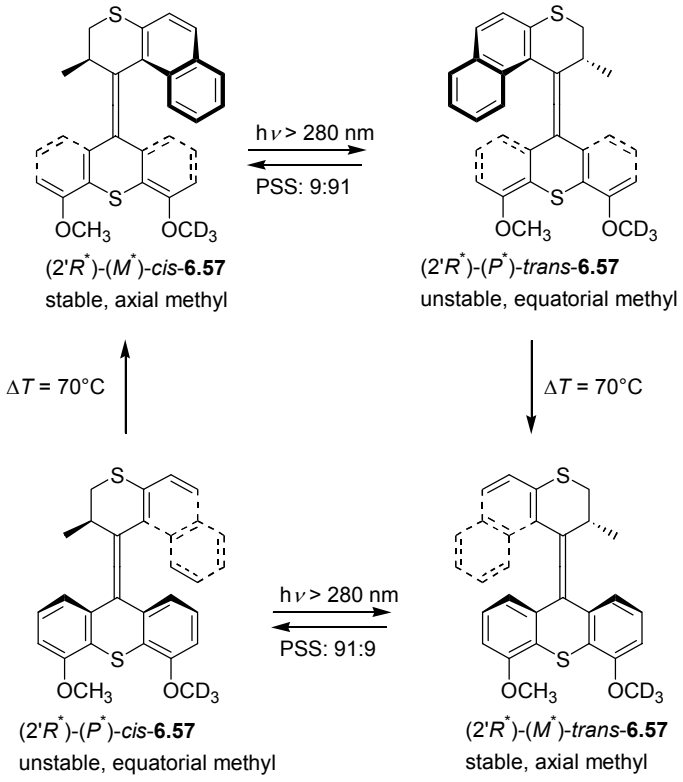
The *cis*- and *trans*-alkenes **6.55** possess, fortunately, a different solubility in, for example, chloroform and heptane/ethyl acetate mixtures and could therefore be separated to a large extent. The *cis*-isomer of **6.55** (based on the position of the acetyl moiety relative the naphthalene moiety in the upper half) proved to be the more soluble of the two stereoisomers. Unfortunately, both isomers could only be obtained pure in very small

amounts. The reaction sequence was therefore continued with isomerically impure compounds. For the *trans*-**6.55** a sample was obtained containing *trans*-**6.55** and *cis*-**6.55** in a ratio of 83:17 and for the *cis*-**6.56** a sample was used containing *cis*-**6.56** and *trans*-**6.56** in a ratio of 80:20. In both isomers the acetyl moiety was removed by reduction using $NaBH_4$ in a mixture of ether and methanol to provide in good yield the *trans*- and *cis*-phenols **6.56**. Both phenols **6.56** react readily with methyl-d_3 iodide to give the deuterium substituted molecular motors *cis*-**6.57** and *trans*-**6.57**. Since isomerically enriched samples were used for the synthesis, *trans*-**6.57** was obtained containing 17% of the *cis*-**6.57** isomer. Similarly, *cis*-**6.57** was obtained containing 20% of the *trans*-**6.57** isomer. The assignment of the *cis* and *trans* structures for motors **6.54**, **6.55** and **6.56** and the position of deuteration of **6.57** was based on the ^{1}H NMR spectra of **6.2** and **6.57**.

6.5.2 ^{1}H NMR Experiments with the Deuterated Motor

In order to demonstrate unequivocally that motor molecule **6.2**, which is symmetrically substituted in the lower half with two methoxy substituents, is able to perform a unidirectional rotation around its central double bond, *cis*-**6.57** and *trans*-**6.57** were successfully synthesized as was described above. Unfortunately, these isomers could not be obtained in pure form and the isomeric excess in both *cis*-**6.57** and *trans*-**6.57** is approximately 80%. The irradiations were therefore performed with samples containing an excess of either *cis*-**6.57** or *trans*-**6.57**. A sample consisting of 80% (2'*R**)-(*M**)-*cis*-**6.57** and 20% (2'*R**)-(*M**)-*trans*-**6.57** was irradiated ($\lambda \geq$ 280 nm, *T*= 0°C) and the conversion to the unstable isomers (2'*R**)-(*P**)-*trans*-**6.57** and (2'*R**)-(*P**)-*cis*-**6.57** was followed by ^{1}H NMR. During the irradiation, a photochemical *cis*-*trans* isomerization takes place switching the naphthalene moiety to the opposite side of the double bond and the methyl substituent changes its orientation from the stable axial orientation to the unstable equatorial orientation. The PSS contained the stable and unstable isomers of **6.57** in a ratio of 9:91 which is the same value already found for the non-deuterated motor molecule **6.2**. This value for the PSS was determined by integration of the absorptions of the stable and unstable isomers of the upper half protons, the protons of the methyl substituent and the aromatic protons at δ 7.6 ppm to δ 7.9 ppm. The absorptions of the methoxy groups shift only slightly and overlap with protons of the lower half. However, detailed analysis revealed that the sample of (2'*R**)-(*M**)-*cis*-**6.57** consisted after the irradiation of (2'*R**)-(*P**)-*trans*-**6.57**, (2'*R**)-(*P**)-*cis*-**6.57**, (2'*R**)-(*M**)-*cis*-**6.57** and (2'*R**)-(*M**)-*trans*-**6.57** in a ratio of 73 : 18 : 7 : 2. Heating (*T*= 70°C) this sample overnight resulted in full conversion of the unstable isomers (2'*R**)-(*P**)-*trans*-**6.57** and (2'*R**)-(*P**)-*cis*-**6.57** to the stable isomers (2'*R**)-(*M**)-*trans*-**6.57** and (2'*R**)-(*M**)-*cis*-**6.57**. The ratio of the (2'*R**)-(*M**)-*cis*-**6.57** and (2'*R**)-(*M**)-*trans*-**6.57** after irradiation and subsequent heating was determined by ^{1}H NMR to be 25:75. The same irradiation experiments were performed with a sample with an excess of the (2'*R**)-(*M**)-*trans*-**6.57** isomer, consisting of 83% (2'*R**)-(*M**)-*trans*-**6.57** and 17% (2'*R**)-(*M**)-*cis*-**6.57**. After irradiation ($\lambda \geq$ 280 nm, *T*= 0°C) a mixture was obtained containing (2'*R**)-(*P**)-*cis*-**6.57**, (2'*R**)-(*P**)-*trans*-**6.57**, (2'*R**)-(*M**)-*trans*-**6.57** and (2'*R**)-(*M**)-*cis*-**6.57** in a ratio of 76 : 15 : 7 : 2. Heating (*T*= 70°C) of this sample also resulted in full conversion to the stable isomers, (2'*R**)-(*M**)-*cis*-**6.57** and (2'*R**)-(*M**)-*trans*-**6.57**, which were obtained in a ratio of 78:22. With these two experiments the full rotary cycle as

is depicted in scheme 6.14 was demonstrated. Either stable isomer of **6.57** can be converted in 91% selectivity in a photochemical step followed by a thermal step resulting in the formation of the other stable isomer of **6.57**. During this process, the respective intermediate unstable isomers of **6.57** are readily detected which confirms the unidirectionality of the rotary process around the central double bond. Since the difference between a protonated or a deuterated methoxy substituent is not significant in these types of *cis-trans* photo-isomerization processes, the unidirectionality of rotation of **6.57** also demonstrates that motor molecules **6.2** and **6.1** are able to perform a unidirectional rotation around the central double bond.



Scheme 6.14 *Rotary cycle for the deuterated analogue **6.57**.*

6.6 Conclusion

In this chapter the design, synthesis, physical properties and rotary behavior of gold colloids functionalized with motor molecules are discussed. Initially, these gold nanoparticles were synthesized in seventeen consecutive steps from 2-amino-3-methoxy-benzoic acid. Later a more efficient route was developed. This route enabled also the

synthesis, in an eleven step sequence, of a deuterated analogue needed to prove the unidirectional rotation for these motor molecules. Furthermore a motor functionalized in the upper half was developed, which enables attachment of a motor molecule via the upper half.

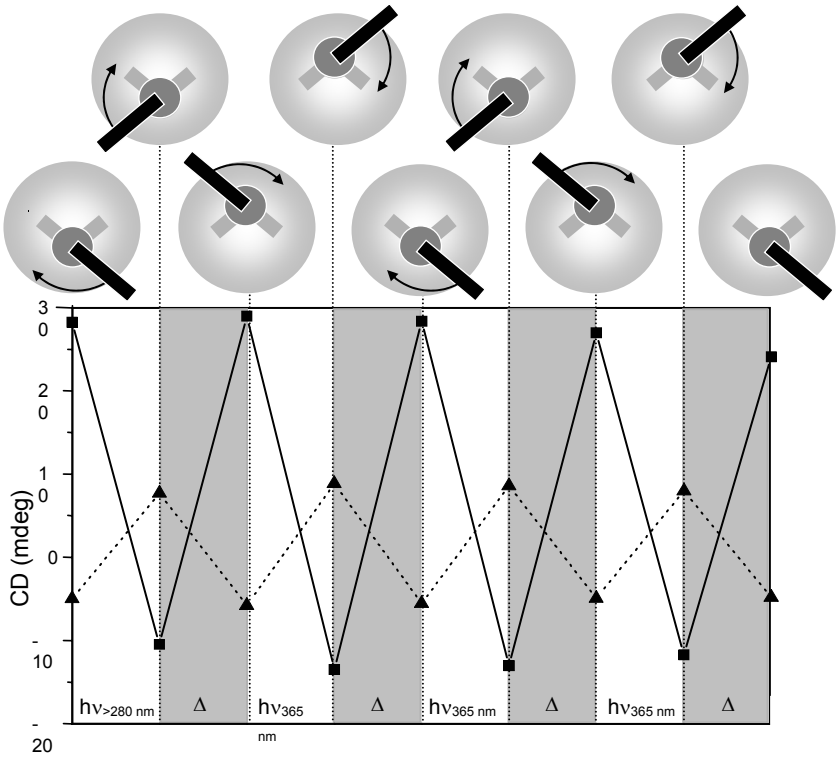


Figure 6.13 *Schematic representation of the unidirectional rotation of* ***6.1*** *(as viewed along the rotation axis) and two full four-stage rotary cycles as determined by CD spectroscopy at 290 nm (solid) and 320 nm (dashed).*

The rotary behavior of the molecular motors was initially investigated with ^{1}H NMR. It was shown that the dimethoxy substituted molecular motor could effectively be converted by irradiation to the unstable isomer and be converted to the more stable isomer by subsequent heating. Since this molecule is symmetrically substituted in the lower half, the unsymmetrically substituted deuterated molecular motor was synthesized. In order to keep the electronic and photochemical properties of the molecule as close as possible to the original dimethoxy substituted molecular motor, three protons were replaced by three deuterons by a highly effective synthetic route. By ^{1}H NMR the unidirectional rotation of this deuterated motor molecule was unequivocally proven allowing to conclude that the

dimethoxy substituted motor molecule and motor molecule attached to the gold nanoparticle also are able to perform this unidirectional rotation around the central double bond. The rotary process for the molecular motor attached to the gold surface was confirmed by UV-Vis and CD spectroscopy. The unidirectional rotation is, as anticipated, attained in two steps in which the *rotor* half of the molecule rotates in a counterclockwise fashion with respect to the *stator* half (figure 6.13). The rotary motion can be extended by performing the same process repeatedly where the state of the molecular motor can be followed by CD spectroscopy. Although the photoequilibria are not perfect, under irradiation at elevated temperature this motor attached to a gold nanoparticle will perform a continuous unidirectional rotation with the central olefinic bond as the rotation axis, functioning in the same way as a free motor. This is a highly promising result in the development in the context of nanoscale molecular machinery since it takes the concept of molecular motors to a new level.

6.7 Experimental Section

General Information

See for general remarks concerning all experimental details chapter 2. Compound **6.38** was prepared according to the procedure reported in chapter 3. Dynamic light scattering (DLS) measurements were performed on a Zetasizer 5000 instrument (Malvern Instruments, Ltd., U.K.). Transmission electron microscopy were performed by drs. C. R. van den Brom. FT-IR measurements were performed with a Nexus FT-IR.

Table 6.1 *X-ray crystallographic data of (2'R,M)-4,5-dimethoxy-9-(2',3'-dihydro-2'-methyl-1'H-naphtho[2,1-b]thiopyran-1'-ylidene)-9H-thioxanthene* ***6.2****.*

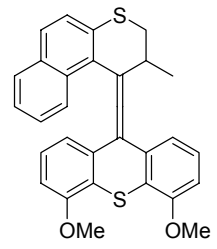
formula	$C_{29}H_{24}O_2S_2$	ρ (g·cm^{-3})	1.309
fw (g·mol^{-1})	468.64	T (K)	110(2)
crystal dimension (mm)	0.13 x 0.11 x 0.09	μ (cm^{-1})	2.49
color, habit	colorless, parallelpiped	number of reflections	11841
crystal system	monoclinic	number of refined	
space group, no.	$P2_1$, 4	parameters	786
a (Å)	8.9625(6)	final agreement factors:	
b (Å)	22.785(2)	$wR(F^2)$	0.0863
c (Å)	11.6435(8)	$R(F)$	0.0420
β (°)	90.127(1)	GooF	1.036
V (Å^3)	2377.7(3)	Flack's refiment	0.01(5)
Z	4		

Motor functionalized Gold Colloids (6.1)

To a mixture of Oct_4NBr (13 mg, 24 μmol) in toluene (1.6 ml) was added a solution of $HAuCl_4 \cdot 3\ H_2O$ (5.5 mg, 13.3 μmol) in water (0.6 ml) giving an orange solution which was stirred for 5 min. Then was added the dithiol **6.31** (4.5 mg, 6.2 μmol) in a small amount of toluene (0.5 ml). The mixture was

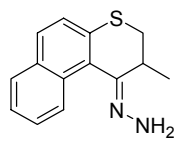
stirred again for 5 min and then a solution of $NaBH_4$ (5 mg, 0.13 mmol) was added immediately giving a black suspension. The reaction mixture was stirred overnight and the organic layer was washed with water (3x 2 ml). The toluene was then removed *in vacuo* and the colloids were dried *in vacuo*. For purification purposes, the colloids were redissolved in toluene (2 ml) and then precipitated with methanol repeatedly giving the pure gold colloids; UV-Vis: (toluene) λ (ε) 296 (28600), 321 (20400), 351 (15200), 526 (3900); CD: (toluene) λ ($\Delta\varepsilon$) 283 (+91.0), 324 (-15.8), 359 (-19.6).

4,5-Dimethoxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.2)



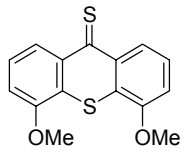
Under a nitrogen atmosphere copper powder (approx. 300 mg) was added to a stirred solution of episulfide **6.23** (232 mg, 0.46 mmol) in *p*-xylene (10 mL). After heating at reflux overnight, the reaction mixture was allowed to cool to room temperature and the brown copper residue was removed by filtration and washed with dichloromethane. The solvents were evaporated under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, hexane:CH_2Cl_2=2:1) to obtain olefin (206 mg, 0.44 mmol, 95%) as a colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.74-0.75 (d, *J*= 6.6, $Me_{2'ax,}$ 3H), 3.05-3.08 (dd, *J*= 11.4, 2.9 Hz, $H_{3'eq}$, 1H), 3.68-3.72 (dd, *J*= 11.4, 7.3 Hz, $H_{3'ax}$, 1H), 3.81 (s, OMe_5, 3H), 4.00 (s, OMe_4, 3H), 4.07-4.15 (dqd, *J*= 7.3, 6.6, 2.9 Hz, $H_{2'eq}$, 1H), 6.03-6.08 (dd, *J* = 7.7, 1.1 Hz, H_8, 1H), 6.28-6.30 (dd, *J* = 8.1, 1.1 Hz, H_6, 1H), 6.36-6.40 (m, H_7, 1H), 6.85-6.88 (dd, *J* = 8.1, 1.1 Hz, H_3, 1H), 7.00-7.04 (m, $H_{8'}$, 1H), 7.09-7.13 (m, $H_{9'}$, 1H), 7.22-7.24 (dd, *J* = 7.7, 1.1 Hz, H_1, 1H), 7.36-7.38 (m, H_2, 1H), 7.40-7.42 (d, *J*= 8.4 Hz, $H_{6'}$, 1H), 7.55-7.58 (d, *J*=8.4 Hz, $H_{7'}$, 1H), 7.59-7.61 (d, *J*= 8.4 Hz, $H_{10'}$, 1H), 7.62-7.64 (d, *J*= 8.4 Hz, $H_{5'}$, 1H); ^{1}H NMR (toluene-d_8, 400 MHz, stable isomer, axial methyl substituent) δ 0.53-0.54 (d, *J*= 6.6 Hz, 3H), 2.67-2.70 (dd, *J*= 11.5, 2.7 Hz, 1H), 3.22 (s, 3H), 3.36 (s, 3H), 3.36-3.41 (m, 1H), 4.06-4.10 (m, 1H), 5.86-5.88 (d, *J*= 8.1 Hz, 1H), 6.16-6.20 (m, 1H), 6.61-6.33 (d, *J*=7 Hz, 1H), 6.39-6.41 (d, *J*= 8.1 Hz, 1H), 6.87-6.91 (m, 1H), 6.97-7.09 (m, 2H), 7.14-7.16 (d, *J*= 7.7 Hz, 1H), 7.31-7.37 (m, 3H), 7.87-7.89 (d, *J*= 8.4 Hz, 1H); ^{1}H NMR (toluene-d_8, 400 MHz, unstable isomer, equatorial methyl substituent) δ 0.89-0.90 (d, *J*= 7.0 Hz, 3H), 2.25-2.31 (m, 1H), 2.98-3.05 (m, 2H), 3.22 (s, 3H), 3.34 (s, 3H), 5.85-5.87 (d, *J*= 8.1 Hz, 1H), 6.14-6.18 (m, 1H), 6.27-6.30 (d, *J*= 7.7 Hz, 1H), 6.35-6.37 (m, 1H), 6.90-7.16 (m, 4H), 7.36-7.44 (m, 3H), 7.73-7.75 (d, *J*= 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1 (q), 32.0 (d), 37.2 (t), 56.0 (2xq), 107.6 (d), 108.2 (d), 119.9 (d), 121.6 (d), 122.7 (s), 124.3 (d), 124.5 (d), 125.4 (d), 125.5 (d), 125.7 (d), 126.5 (d), 127.3 (d), 127.4 (d), 130.8 (s), 131.3 (s), 131.6 (s), 132.2 (s), 134.7 (s), 136.3 (s), 136.5 (s), 138.8 (s), 155.2 (s), 156.1 (s), one (s) signal was not observed; *m/z* (EI, %) = 468 (M^+, 100); HRMS (EI): calcd. for $C_{29}H_{24}O_2S_2$: 468.1218, found 468.1208; Synthesis yielded two enantiomers of **6.2** ((2'*R*)-(*M*)-**6.2** and (2'*S*)-(*P*)-**6.2**) which were resolved by preparative chiral HPLC employing a Chiralcel AD column as the stationary phase and *n*-heptane : *i*-propanol 9:1 as the eluent (1 ml·min^{-1}). The first eluted fraction (*t*= 5.1 min) was assigned by X-ray crystallography and CD spectroscopy to be (2'*R*)-(*M*)-**6.2** and second eluted fraction (*t*= 6.4 min) was assigned to be (2'*S*)-(*P*)-**6.2**. The fraction containing the (2'*R*)-(*M*) isomer of **6.2** was used for all chiroptical studies on compound. The absolute configuration of the molecule chosen for the molecule was determined by Flack's refinement (**x**= 0.01(5); UV-Vis and CD spectroscopic data for pure stable (2'*R*)-(*M*)-**6.2**: UV-Vis: (toluene) $\lambda_{max}(\varepsilon)$ 295 (16300), 323 (10500), 350 (shoulder, 6400); CD: (toluene) $\lambda_{max}(\Delta\varepsilon)$ 283 (+92.6), 322 (-15.2), 351 (-18.6); CD: (*n*-dodecane) λ ($\Delta\varepsilon$) 202 (+31.4), 214 (-67.5), 241 (-5.4), 251 (-46.0), 281 (+92.0), 321 (-14.8), 349 (-18.8); UV-Vis and CD spectroscopic data for pure unstable (2'*R*)-(*P*)-**6.2**: UV-Vis (calc., toluene) $\lambda_{max}(\varepsilon)$ 295 (16900), 315 (10900), 347 (shoulder, 3900); CD: (calc., toluene) $\lambda_{max}(\Delta\varepsilon)$ 283 (-66.0), 318 (+26.2), 345 (+13.5)

2,3-Dihydro-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1-one hydrazone (6.3)



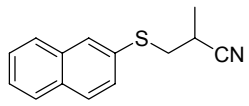
A mixture of ketone **6.8** (3.37 g, 14.8 mmol), hydrazine monohydrate (20 ml) and ethanol (20 ml) was heated at reflux overnight. After cooling, water (100 ml) was added and the mixture was extracted with ethyl acetate (3x 50 ml). The combined organic layers were washed with brine (3x 100 ml), dried (Na_2SO_4) and then all volatiles were removed to give a yellow solid. This solid was rinsed with a small amount of ethyl acetate and then recrystallized from ether to give the hydrazone as slightly yellow crystals (1.36 g, 5.6 mmol, 38%); ^{1}H (300 MHz, $CDCl_3$) δ 1.31-1.34 (d, *J*= 7.0 Hz, 3H), 2.67-2.74 (dd, *J*= 12.8, 9.5 Hz, 1H), 317-3.23 (dd, *J*= 12.8, 5.9 Hz, 1H), 3.47-3.58 (ddq, 9.5, 5.9, 7.0 Hz, 1H), 5.5 (bs, 2H), 7.33-7.36 (d, *J*= 8.4 Hz, 1H), 7.38-7.43 (m, 1H), 7.46-7.51 (m, 1H), 7.63-7.66 (d, *J*= 8.8 Hz, 1H), 7.75-7.77 (d, *J*= 7.3 Hz, 1H), 8.41-8.43 (d, *J*= 8.4 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 14.6 (q), 33.8 (d), 36.3 (t), 125.0 (d), 125.9 (d), 126.1 (d), 126.6 (d), 126.6 (d), 127.6 (d), 127.9 (d), 130.7 (s), 132.0 (s), 132.9 (s), 135.6 (s), 149.1 (s); *m/z* (EI, %) = 242 (M^+, 100); HRMS (EI): calcd. for $C_{14}H_{14}N_2S$: 242.0884, found 242.0878.

4,5-Dimethoxy-9*H*-thioxanthene-9-thione (6.4)



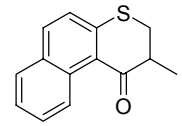
A mixture of 4,5-dimethoxy-9*H*-thioxanthene-9-one **6.16** (417 mg, 1.52 mmol) and P_4S_{10} (2.04 g, 4.59 mmol) in 25 mL of toluene was refluxed for 2h. The deep green reaction mixture was filtered, and the residues were washed with CH_2Cl_2. The crude product, obtained after evaporation of all volatiles, was purified by column chromatography (SiO_2. toluene:CH_2Cl_2 = 1:1) and finally recrystallized from toluene to yield dark green needles of the thioketone **6.4** (430 mg, 1.49 mmol, 97%); m.p. 259.2-259.5 ºC; ^{1}H (300 MHz, $CDCl_3$) δ 4.06 (s, 6H), 7.11-7.14 (d, *J*= 7.7 Hz, 2H), 7.37-7.42 (m, 2H), 8.65-8.68 (dd, *J*= 8.6, 0.9 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 56.6 (q), 111.2 (d), 123.1 (s), 125.3 (d), 126.4 (d), 138.3 (s), 155.0 (s), due to low solability, the no signal for the thiocarbonyl carbon atom was observed; *m/z* (EI, %) = 288 (M^+, 100), 273 (48); HRMS (EI): calcd. for $C_{15}H_{12}O_2S_2$: 288.0279, found 288.0268; ele. anal., calc. (%): C, 62.47; H, 4.19; S, 22.24; found (%): C, 61.98; H, 4.02; S, 22.43.

2-Methyl-3-(naphthalen-2-ylsulfanyl)-propionitrile (6.7)



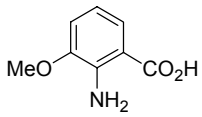
To methacrylonitrile (200 ml) cooled to -40°C was added dropwise Triton B (0.4 ml). The mixture was stirred for an additional 15 min whereupon naphthalenethiol (20 g, 125 mmol) was added. The mixture was allowed to reach gradually room temperature and was then heated at reflux overnight. The reaction mixture was then poured into a sat. aq. sol. of NH_4Cl (500 ml) and extracted with ether (2x 300 ml). The combined organic layers were washed with brine (3x 400 ml), dried ($MgSO_4$) and all volatiles were removed under reduced pressure giving a yellow oil (27.0 g, 119 mmol, 95%) sufficiently pure to perform subsequent reactions; ^{1}H (300 MHz, $CDCl_3$) δ 1.36-1.39 (d, *J*= 7.0 Hz, 3H), 2.69-2.77 (m, 1H), 3.00-3.06 (dd, *J*= 13.9, 7.3 Hz, 1H), 3.19-3.26 (dd, *J*= 13.6, 7.3 Hz, 1H), 7.39-7.48 (m, 3H), 7.72-7.83 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 17.0 (q), 25.9 (d), 37.6 (t), 121.3 (s), 126.1 (d), 126.6 (d), 127.0 (d), 127.5 (d), 127.9 (d), 128.7 (d), 129.3 (d), 131.1 (s), 132.0 (s), 133.4 (s); *m/z* (EI, %) = 227 (M^+, 67), 173 (100); HRMS (EI): calcd. for $C_{14}H_{13}NS$: 227.0769, found 227.0764.

2,3-Dihydro-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1-one (6.8)



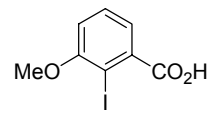
The nitrile **6.6** (26.5 g, 117 mmol) was added to PPA (250 ml) stirred at 60°C. The temperature was then raised to 110°C and stirring was continued for 3h. The reaction mixture was poured onto ice (500 g) and allowed to hydrolyze overnight. The aqueous layer was extracted with ether (3x 200 ml), dried ($MgSO_4$) and after evaporation of the organic volatiles the ketone was obtained as a yellow oil which was purified by column chromatography (SiO_2, heptane:ethyl acetate= 16:1, R_f= 0.50) to yield the desired ketone (23.2 g, 102 mmol, 87%); ^{1}H (300 MHz, $CDCl_3$) δ 1.39-1.42 (d, *J*= 6.6 Hz, 3H), 3.08-3.29 (m, 3H), 7.23-7.26 (d, *J*= 8.8 Hz, 1H), 7.42-7.47 (m, 1H), 7.56-7.61 (m, 1H), 7.73-7.79 (m, 2H), 9.06-9.09 (d, *J*= 8.4 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 15.2 (q), 32.6 (t), 42.7 (d), 124.9 (d), 125.1 (s), 125.4 (d), 125.6 (d), 128.3 (d), 128.8 (d), 131.5 (s), 132.3 (s), 133.1 (d), 143.9 (s), 199.1 (s); *m/z* (EI, %) = 228 (M^+, 41), 186 (100); HRMS (EI): calcd. for $C_{14}H_{12}OS$: 228.0609, found 228.0622.

2-Amino-3-methoxybenzoic acid (6.9)



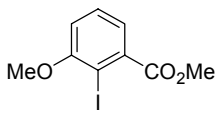
Under a nitrogen atmosphere palladium on activated carbon (3%, 100mg) was added to a solution of 3-methoxy-2-nitro-benzoic acid **6.5** (1.03 g, 5.22 mmol) in ethanol (60 mol). The reaction mixture was purged three times with hydrogen and was then stirred overnight at room temperature. After filtration of the palladium carbon, the ethanol was removed under the reduced pressure. The crude product was recrystallized from ethanol to yield colorless needles (780 mg, 4.67 mmol, 90%); m.p. 169.6-171.4°C (lit. 169-170°C, 171-172°C);[21] ^{1}H (300 MHz, DMSO-d_6) δ 3.78 (s, 3H), 6.45-6.51 (m, 1H), 6.92-6.95 (d, *J*= 7.7 Hz, 1H), 7.30-7.33 (dd, *J*= 8.1, 1.5 Hz, 1H), 8.5 (br s, 2H); ^{13}C (75 MHz, DMSO-d_6) δ 55.7 (q), 109.5 (s), 113.3 (s), 113.8 (d), 122.6 (d), 141.9 (s),146.8 (s), 169.8 (s); *m/z* (EI, %) = 167 (M^+, 100); an exact mass of this compound could not be obtained.

2-Iodo-3-methoxy-benzoic acid (6.10)



A mixture of ester **6.12** (0.81 g, 2.8 mmol) suspended in methanol (30 ml), water (10 ml) and LiOH (1.0 g, 42 mmol) was stirred overnight at room temperature. The reaction mixture was then acidified with an aq. sol. of 30% HCl (50 ml) and extracted with ether (3x 75 ml). The combined organic layers were washed with water (2x 100 ml) and brine (2x 100 ml), dried ($MgSO_4$) and gave after removal of all volatiles acid **6.10** as a white solid (0.72 g, 2.59 mmol, 92%); m.p. 146.5-149-6°C (lit. 148-149°C)[22]; ^{1}H (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.98-7.00 (dd, *J*= 8.0, 1.5 Hz, 1H), 7.36-7.41 (m, 1H), 7.46-7.49 (dd, *J*= 7.7, 1.5 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 56.9 (q), 87.5 (s), 114.1 (d), 123.6 (d), 129.3 (d), 136.7 (s), 158.9 (s), 172.3 (s); *m/z* (EI, %) = 278 (M^+, 100), 261 (21); HRMS (EI): calcd. for $C_8H_7IO_3$: 277.9440, found 277.9437.

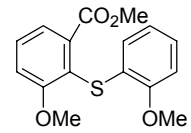
2-Iodo-3-methoxy-benzoic acid methyl ester (6.12)



To an ice cooled suspension of 2-amino-3-methoxy-benzoic acid **6.9** (2.00 g, 12.0 mmol) in 40 ml of an aq. sol. of 20% HCl was added dropwise an ice-cooled solution of $NaNO_2$ (1.0 g, 14.5 mmol) in water (20 ml). After being stirred for 15 min at 0°C, the clear orange solution was poured slowly into a two-phase mixture of CH_2Cl_2 (50 ml) and KI (6.0 g, 36mmol) dissolved in

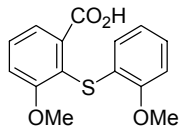
water (50 ml) cooled at 0°C. Stirring was continued for 4h at room temperature. Then, ether was added (100 ml) and the combined organic layers were washed with a dilute sol. aq. sol. of $NaHSO_3$ (2x 100 ml), water (2x 100 ml) and brine (100 ml) and dried over $MgSO_4$. Evaporation of all volatiles gave a beige solid (2.52 g) to which were added a mixture of DMF (25 ml), methyl iodide (2.0 ml, 32 mmol) and K_2CO_3 (2.0 g, 20 mmol) and stirred overnight. Ether (100 ml) was added to the mixture and the organic layer was washed with brine (5x 100 ml) and dried ($MgSO_4$). From the oil obtained after removal of all volatiles was seperated by column chromatography (SiO_2, heptane:ethyl acetate= 16 :1, R_f= 0.20) the desired **6.12** as a slightly colored solid (2.25 g, 7.71 mmol, 64% over 2 steps); 53.2-55.4°C (lit. 56-57°C)[22]; ^{1}H (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 3.94 (s, 3H), 6.91-6.94 (dd, *J*= 8.2 Hz, 1H), 7.21-7.24 (dd, *J*= 7.7, 1.5 Hz, 1H), 7.32-7.37 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 52.2 (q), 56.4 (q), 86.0 (s), 112.7 (d), 121.8 (d), 129.0 (d), 138.4 (s), 158.1 (s), 167.5 (s); *m/z* (EI, %) = 292 (M^+, 100), 261 (71); HRMS (EI): calcd. for $C_9H_9IO_3$: 291.9597, found 291.9607.

3-Methoxy-2-(2-methoxy-phenylsulfanyl)-benzoic acid methyl ester (6.14)



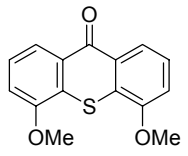
A mixture of acid **6.10** (2.90 g, 10.4 mmol), thiol **6.13** (1.90 g, 12.2 mmol), copper powder (200 mg, 3.1 mmol) and K_2CO_3 (5.0 g, 50 mmol) in DMF (125 ml) was refluxed for 7h. After cooling to room temperature, methyl iodide (5.0 ml, 80 mmol) was added and stirring was continued overnight. Water (300 ml) was added followed by extraction with ether (3x 100 ml). The combined organic layers were washed with water (7x 200 ml) and dried ($MgSO_4$). The oil obtained after removal of all volatiles was purified by column chromatography (SiO_2, heptane:ethyl acetate=4:1, R_f= 0.29) to yield **6.14** (2.27 g, 7.48 mmol, 72%) as a white solid; m.p. 118.3-118.6°C; ^{1}H (300 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.79 (s, 3H), 3.86 (s, 3H), 6.70-6.78 (m, 2H), 6.80-6.83 (d, *J*= 8.1 Hz, 1H), 7.01-7.04 (d, *J*= 8.1 Hz, 1H), 7.06-7.11 (m, 1H), 7.22-7.24 (dd, *J*= 7.7, 1.1 Hz, 1H), 7.38-7.44 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 51.9 (q), 55.4 (q), 55.9 (q), 110.0 (d), 113.2 (2xd), 118.7 (s), 120.5 (d), 125.3 (s), 126.0 (d), 127.4 (d), 129.9 (d), 139.6 (s), 155.7 (s), 159.9 (s), 167.9 (s); *m/z* (EI, %) = 304 (M^+, 100); HRMS (EI): calcd. for $C_{16}H_{16}O_4S$: 304.0769, found 304.0778; ele. anal., calc. (%): C, 63.1; H, 5.30; S, 10.54; found (%): C, 62.9; H, 5.46; S, 10.54.

3-Methoxy-2-(2-methoxy-phenylsulfanyl)-benzoic acid (6.15)



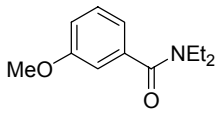
Following the procedure for the hydrolysis of ester **6.12**, ester **6.15** (2.27 g, 7.47 mmol) was subjected to a mixture of methanol (90 ml), water (30 ml) and LiOH (5.0 g, 0.2 mol) overnight at room temperature. The acid was obtained after workup as a colorless solid (1.92 mmol, 6.62 mmol, 89%); m.p. 160.0-162.4°C; ^{1}H (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.82 (s, 3H), 6.83-6.89 (m, 2H), 7.03-7.06 (d, *J*= 8.1 Hz, 1H), 7.20-7.24 (m, 2H), 7.41-7.46 (m, 1H), 7.67-7.69 (d, *J*= 8.1 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 55.7 (q), 56.2 (q), 110.7 (d), 114.5 (d), 119.8 (s), 121.0 (d), 123.0 (d), 123.3 (s), 128.0 (d), 130.1 (d), 130.9 (d), 136.8 (s), 156.9 (s), 170.2 (s); *m/z* (EI, %) = 290 (M^+, 100); HRMS (EI): calcd. for $C_{15}H_{14}O_4S$: 290.0613, found 290.0617; ele. anal., calcd (%): C, 62.1; H, 5.05; S, 11.04; found (%): C, 61.7; H, 5.05; S, 11.57.

4,5-Dimethoxy-9*H*-thioxanthen-9-one (6.16)



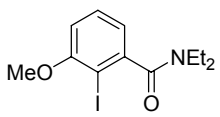
Method A: To PPA (10 ml) stirred at 60°C was added acid **6.15** (0.22 g, 0.76 mmol). The temperature was raised to 110°C and stirring of the now dark red solution was continued for 3h. The hot PPA was then poured into water (100 ml) and hydrolyzed by stirring overnight. The water was extracted with ether (3x 50 ml) and the combined organic layers were washed with brine (2x 100 ml), dried ($MgSO_4$) and then all volatiles were removed under reduced pressure giving the ketone **6.16** as a slightly yellow solid (0.17 g, 0.63 mmol, 82%); Method B: To a freshly prepared solution of LDA (17.6 mmol) in THF (50 ml) at 0°C was added dropwise amide **6.20** (1.20 g, 3.48 mmol) dissolved in THF (25 ml). Upon completion of the addition, the ice bath was removed and the yellow solution was stirred at room temperature for 1h. A sat. sol. of NH_4Cl (100 ml) was added followed by extraction with ether (3x 100 ml). The crude product was obtained after drying over Na_2SO_4 and evaporation of all volatiles. Purification was performed by flash column chromatography (SiO_2, heptane:ethyl acetate) giving the desired compound as a slightly yellow solid (0.92 g, 3.38 mmol, 97%); m.p.>250°C; ^{1}H (300 MHz, $CDCl_3$) δ 4.05 (s, 6H), 7.13-7.15 (d, *J*= 7.7 Hz, 2H), 7.42-7.47 (m, 2H), 8.23-8.26 (dd, *J*= 8.2, 0.9 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 56.4 (q), 112.1 (d), 121.4 (d), 125.9 (d), 127.6 (s), 129.9 (s), 154.8 (s), 180.2 (s); *m/z* (EI, %) = 272 (M^+, 100), 257 (46); HRMS (EI): calcd. for $C_{15}H_{12}O_3S$: 272.0507, found 272.0506; ele. anal., calc. (%): C, 66.2; H, 4.44; S, 12.44; found (%): C, 66.3; H, 4.41; S, 11.77.

***N*,*N*-Diethyl-3-methoxy-benzamide (6.17)**



To 3-methoxybenzoic acid (19.0 g, 125 mmol) dissolved in CH_2Cl_2 (100 ml) was added $SOCl_2$ (22 ml, 36 g, 0.3 mol) and a drop of DMF. After refluxing this mixture for 1h, the solution was cooled down to 0°C and diethylamine (13.6 ml, 9.5 g, 130 mmol) and triethylamine were added carefully (18 ml, 13 g, 130 mmol). While stirring, the reaction mixture was allowed to reach room temperature. After quenching the reaction with water (300 ml) after 2h and addition of extra CH_2Cl_2 (100 ml), the organic layer was extracted with an aq. sol. of 10% HCl (2x 200 ml) and a sol. of 1*N* NaOH (2x 200ml). After drying ($MgSO_4$) and removal of all volatiles, the desired amide **6.17** was obtained as a slightly yellow oil (23.8 g, 115 mmol, 92%); ^{1}H (300 MHz, $CDCl_3$) δ 1.17 (br s, 3H), 1.29 (br s, 3H), 3.59 (br s, 2H), 3.85 (br s, 2H), 3.87 (s, 3H), 6.96-7.00 (m, 3H), 7.32-7.35 (d, *J*= 8.8 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 12.5 (q), 13.9 (q), 38.8 (t), 42.9 (t), 54.8 (q), 111.3 (d), 114.5 (d), 117.9 (d), 129.1 (d), 138.1 (s), 159.1 (s), 170.5 (s); *m/z* (EI, %) = 207 (M^+, 38), 135 (100); HRMS (EI): calcd. for $C_{12}H_{17}NO_2$: 207.1259, found 207.1257.

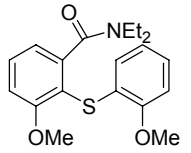
***N*,*N*-Diethyl-2-iodo-3-methoxy-benzamide (6.19)**



To THF (50 ml) cooled to –80°C was added TMEDA (2.4 ml, 16.5 mmol) and *s*-BuLi (12.7 ml, 16.5 mmol). After stirring for 15 min, a solution of amide **6.16** was added dropwise and stirring was continued for 1h at –80°C giving a yellow suspension. Iodine (20 g, 79 mmol) was added and the reaction mixture was allowed to reach room temperature overnight. Ether (150 ml) was added, followed by washing with a dilute aq. sol. of $NaHSO_3$ (2x 250 ml), 1*N* aq. HCl (2x 150 ml) and drying over Na_2SO_4. After evaporation of the solvents, the brown oil was purified by column chromatography (SiO_2, first heptane:ethyl acetate=16:1 then pure ethyl acetate) to yield iodine **6.19** as a slightly yellow oil (3.59 g, 10.8 mmol, 72%); ^{1}H (300 MHz, $CDCl_3$) δ 1.04-1.09 (t, *J*= 7.1 Hz, 3H), 1.27-1.32 (t, *J*= 7.1 Hz, 3H), 3.09-3.17 (dq, *J*= 7.1, 3.0 Hz, 2H), 3.23 (m, 1H), 3.78-

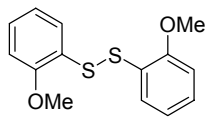
3.90 (m, 1H), 3.90 (s, 3H), 6.77-6.83 (m, 2H), 7.30-7.36 (m, 1H); ^{13}C (75.48 MHz, $CDCl_3$) δ 12.1 (q), 13.5 (q), 38.4 (t), 42.3 (t), 56.2 (q), 84.7 (s), 110.1 (d), 118.7 (d), 129.5 (d), 144.3 (s), 157.7 (s), 169.5 (s); *m/z* (EI, %) = 333 (M^+, 73), 332 (55), 261 (100); HRMS (EI): calcd. for $C_{12}H_{16}INO_2$: 333.0226, found 333.0202.

_N,N_-Diethyl-3-methoxy-2-(2-methoxy-phenylsulfanyl)-benzamide (6.20)



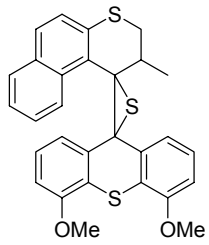
Method A: To THF (50 ml) cooled to –80°C were added *s*-BuLi (2.5 ml, 3.3 mmol) and TMEDA (0.48 ml, 3.3 mmol). After stirring for 30 min, amide **6.16** (0.62 g, 3.0 mmol) dissolved in THF (10 ml) was added and stirring was continued for 1h. To the then yellowish suspension was added at –80°C disulfide **6.21** (1.52 g, 5.47 mmol) and stirring was continued overnight. Addition of ether (100 ml) followed by washing with an aq. 1*N* NaOH sol. (2x 100 ml) and drying of the organic layers (Na_2SO_4) gave after removal of all volatiles under reduced pressure a colorless oil. This oil was purified by column chromatography (SiO_2, heptane:ethyl acetate=2:1, R_f=0.14) and gave **6.20** as a white solid (0.84 g, 2.52 mmol, 84%); Method B: A mixture of **6.19** (2.95 g, 8.86 mmol), thiol **6.13** (1.4 g, 10 mmol), K_2CO_3 (1.4 g, 10 mmol) and copper powder (100 mg, 1.6 mmol) in DMF (25 ml) was refluxed overnight. Addition of ether (200 ml) followed by extensive washing with water (7x 200 ml) gave after drying (Na_2SO_4) and evaporation the crude product which was purified by column chromatography (SiO_2, heptane:ethyl acetate=2:1, R_f=0.14) to give **6.20** as a white solid (1.52 g, 4.41 mmol, 50%); m.p. 140.9-142.6°C; ^{1}H (300 MHz, $CDCl_3$) δ 0.96-1.00 (t, *J*= 7.1 Hz, 3H), 1.16-1.21 (t, *J*= 7.1 Hz, 3H), 2.96-3.15 (m, 2H), 3.31-3.38 (m, 1H), 3.63-3.78 (m, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 6.67-6.76 (m, 2H), 6.78-6.81 (d, *J*= 8.4 Hz, 1H), 6.93-6.95 (m, 2H), 7.02-7.07 (m, 1H), 7.41-7.46 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) *δ* 12.1 (q), 13.6 (q), 38.2 (t), 42.4 (t), 55.4 (q), 55.8 (q), 109.9 (d), 111.0 (d), 115.6 (s), 118.3 (d), 120.6 (d), 125.1 (s), 125.5 (d), 126.5 (d), 130.9 (d), 144.8 (s), 155.3 (s), 160.3 (s), 168.4 (s); *m/z* (EI, %) = 345 (M^+, 100), 273 (74); HRMS (EI): calcd. for $C_{19}H_{23}NO_3S$: 345.1399, found 345.1390; ele. anal., calc. (%): C, 66.1; H, 6.71; N, 4.05; S, 9.28; found (%): C, 66.0; H, 6.78; N, 4.04; S, 9.42.

Di(2-methoxyphenyl)disulfide (6.21)



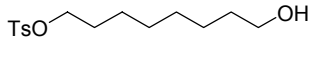
Following a literature procedure,[13] a mixture of $CuSO_4 \cdot 5\ H_2O$ (2.5 g, 10 mmol), $KMnO_4$ (2.5 g, 16 mmol), tetraoctylammonium bromide (0.5 g, 0.9 mmol) and 2-methoxybenzenethiol (1.0 g, 7.1 mmol) in CH_2Cl_2 (100 ml) was stirred for 3h at room temperature. The solids were removed by filtration over celite and the desired compound was subsequently obtained pure by flash column chromatography (SiO_2, heptane:ethyl acetate) as a white solid (0.86 g, 3.1 mmol, 87%); 119.3-120.5°C; ^{1}H (300 MHz, $CDCl_3$) *δ* 3.90 (s, 3H), 6.84-6.86 (d, *J*= 8.1 Hz, 1H), 6.88-6.94 (m, 1H), 7.16-7.22 (m, 1H), 7.52-7.55 (dd, *J*= 7.7, 1.5 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) *δ* 55.6 (q), 110.3 (d), 121.1 (d), 124.2 (s), 127.3 (d), 137.6 (d), 156.4 (s); *m/z* (EI, %) = 278 (M^+, 100); HRMS (EI): calcd. for $C_{14}H_{14}O_2S_2$: 278.0435, found 278.0440.

Dispiro[2,3-dihydro-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1,2'-thiirane-3',9''-(4'',5''-dimethoxy-9''*H*-thioxanthene)] (6.23)



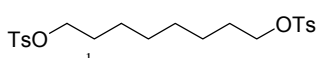
Under a nitrogen atmosphere, a solution of hydrazone **6.3** (273 mg, 0.98 mmol) in dry dichloromethane (10 mL) was cooled to 0°C. $MgSO_4$ (approximately 400 mg), Ag_2O (454 mg, 1.96 mmol) and a sat. sol. of KOH in methanol (0.5 ml) were added subsequently. The mixture was stirred for 5 min at 0°C when the color of the mixture turned red. After stirring for 30 min at 0°C, the deep red suspension was filtered into another ice-cooled bulb and the remaining residue was washed with cold dichloromethane. To the deep red solution was added a solution of thioketone **6.4** (283 mg, 0.98 mmol) in dichloromethane. Nitrogen evolution was observed and the red color of the solution slowly disappeared. The reaction mixture was stirred overnight while the temperature of the reaction mixture was allowed to reach room temperature. All volatiles were removed under reduced pressure to obtain the crude product. An excess of thioketone was removed by column chromatography (SiO_2, hexane:ethyl acetate = 16:1, R_f= 0.20), and the residue was purified by column chromatography (SiO_2, hexane:CH_2Cl_2 = 2:1, R_f= 0.18). After recrystallization from a hexane/CH_2Cl_2 mixture, the episulfide **7.23** was obtained as colorless silky needles (232 mg, 0.46 mmol, 47%), which consisted of only one of the two possible stereoisomers; m.p. 226.9-227.0 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14-1.16 (d, J = 6.6 Hz, 3H), 2.14-2.19 (m, 1H), 2.54-2.69 (m, 2H), 3.79 (s, 3H), 3.98 (s, 3H), 6.15-6.20 (m, 1H), 6.31-6.34 (d, J = 6.9 Hz, 1H), 6.39-6.42 (dd, J = 8.1, 0.9 Hz, 1H), 6.87-6,89 (d, J = 8.1 Hz, 1H), 6.97-7.00 (d, J = 8.4 Hz, 1H), 7.22-7.37 (m, 3H), 7.45-7.51 (m, 1H), 7.59-7.62 (d, J = 8.1 Hz, 1H), 7.68-7.71 (dd, J = 7.8, 0.6 Hz, 1H), 8.77-8.80 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.9 (q), 35.5 (t), 40.7 (d), 56.1 (q), 56.2 (q), 61.7 (s), 65.3 (s), 107.9 (d), 108.5 (d), 122.0 (d), 122.8 (s), 123.3 (d), 124.0 (d), 124.1 (d), 124.4 (d), 125.05 (d), 125.13 (d), 125.8 (d), 126.8 (d), 128.06 (s), 128.13 (d), 131.5 (s), 131.6 (s), 132.2 (s), 134.7 (s), 140.1 (s), 153.9 (s), 154.8 (s), one (s) signal could not be observed; *m/z* (DEI, %) = 500 (M^+, 88), 468 (100).

8-Hydroxy-1-tosyl-octane (6.25)



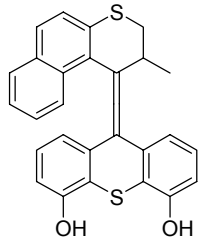
Under a nitrogen atmosphere, 1,8-octanediol (1.54 g, 10.53 mmol) and pyridine (1.70 mL, 21.06 mmol) were dissolved chloroform (15 ml). After being cooled to 0ºC, tosyl chloride (2.41 g, 12.64 mmol) was added to this solution. The reaction mixture was stirred overnight at room temperature. The reaction was quenched with water (100 ml), and the water layer was extracted with ethyl acetate (3x 50 ml). The combined organic layer was washed with an aq. sol. of 10% HCl (100 ml) and a sat. aq. sol. of $NaHCO_3$ (100 ml), and dried over $MgSO_4$. The solvent was evaporated under the reduced pressure to obtain the crude product. The crude product was purified by column chromatography (SiO_2, hexane:ethyl acetate = 3:1, $R_f$ditosyl= 0.55, $R_f$monotosyl= 0.19) to give ditosylate (first fraction, 1.11 g, 2.44 mmol, 23%) as a white solid and monotosylate (second fraction, 1.52 g, 5.05 mmol, 48%) as a colorless oil; ^{1}H (400 MHz, $CDCl_3$) δ 1.24-1.32 (m, 8H), 1.50-1.53 (m, 2H), 1.61-1.65 (m, 2H), 2.45 (s, 3H), 3.61 (t, J= 6.6 Hz, 2H), 4.00-4.03 (t, J= 6.6 Hz, 2H), 7.33-7.36 (d, J= 8.1 Hz, 2H), 7.78-7.80 (d, J= 8.1 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 21.4 (q), 25.0 (t), 25.4 (t), 28.5 (t), 28.6 (t), 28.9 (t), 32.4 (t), 62.4 (t), 70.5 (t), 127.6 (d), 129.6 (d), 132.8 (s), 144.5 (s); HRMS (EI): calcd. for $C_{15}H_{24}O_4S$: 300.1395, found 300.1405.

1,8-Ditosyl-octane (6.26)



Obtained as a side product in the synthesis of monotosylate **6.25** and had the following characteristics: white solid; m.p. 83.4-84.0°C; ^{1}H (400 MHz, $CDCl_3$) δ 1.17-1.28 (m, 8H), 1.57-1.64 (m, 4H), 2.45 (s, 6H), 3.98-4.02 (t, *J*= 6.4 Hz, 4H), 7.33-7.36 (d, *J*= 8.6 Hz, 4H), 7.77-7.80 (d, *J*= 8.6 Hz, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 21.5 (q), 25.0 (t), 28.5 (t), 28.6 (t), 70.5 (t), 127.7 (d), 129.7 (d), 132.9 (s), 144.6 (s); HRMS (EI): calcd. for $C_{22}H_{30}O_6S_2$: 454.1484, found 454.1488; ele. ana., calc. (%): C, 58.1; H, 6.65; S, 14.11; found (%): C, 58.7; H, 6.82; S, 13.91.

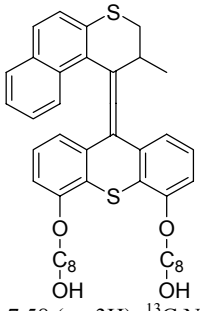
4,5-Dihydroxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.27)



Under a nitrogen atmosphere BBr_3 (0.06 mL, 0.63 mmol) was added to the solution of 4,5-dimethoxy olefin **6.2** (100 mg, 0.21 mmol) in dichloromethane at 0ºC. After stirring overnight at room temperature, the reaction was quenched by adding water. The water layer was extracted with CH_2Cl_2 (twice) and the combined organic layer was washed with water and brine, and dried over Na_2SO_4. The solvent was evaporated under the reduced pressure to obtain the crude product. The product was further purified by column chromatography (SiO_2, heptane:ethyl acetate=2:1, R_f=0.28) giving the bisphenol as a yellow powder (88 mg, 20 mmol, 95%); ^{1}H (400 MHz, $CDCl_3$) δ 0.81-0.83 (d, *J*= 6.6, 3H), 3.04-3.08 (dd, *J*= 11.7, 3.3 Hz, 1H), 3.66-3.71 (dd, *J*= 11.4, 7.3 Hz, 1H), 4.16-4.21 (m, 1H), 5.29 (s, 1H), 5.30 (s, 1H), 6.01-6.03 (dd, *J*= 6.0, 2.7 Hz, 1H), 6.35-6.40 (m, 2H), 6.92-6.94 (dd, *J*= 8.1, 1.1 Hz, 1H), 7.04-7.08 (m, 1H), 7.12-7.15 (m, 1H), 7.22-7.32 (m, 2H), 7.36-7.40 (d, *J*= 8.4 Hz, 1H), 7.55-7.63 (m, 3H); ^{13}C (400 MHz, $CDCl_3$) δ 19.2 (q), 32.5 (d), 37.0 (t), 112.7 (d), 113.7 (d), 119.3 (s), 120.2 (d), 121.0 (s), 121.7 (d), 124.3 (d), 124.5 (d), 125.4 (d), 125.7 (d), 126.9 (d), 127.5 (d), 127.6 (d), 127.9 (d), 130.9 (s), 131.2 (s), 131.4 (s), 132.7 (s), 134.9 (s), 137.1 (s), 139.1 (s), 141.2 (s), 151.6 (s), 152.9 (s); *m/z* (EI, %) = 440 (M^+, 100), 242 (45); HRMS (EI): calcd. for $C_{27}H_{20}O_2S_2$: 440.0905, found 440.0889.

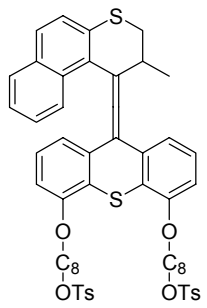
4,5-Bis[(8-hydroxyoctyl)oxy]-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.28)

A mixture of **6.27** (92 mg, 0.21 mmol), monotosylate **6.25** (0.63 mmol, 189 mg) and Cs_2CO_3 (0.63 mmol, 205 mg) in DMF (10 ml) was heated up to 65ºC for 2 days. After cooling to room temperature, water (50 ml) was added and the reaction mixture was extracted with ethyl acetate (3x 25 ml). The combined organic layers were washed with an aq. sol. of 10% HCl (50 ml), water (2x 50 ml), a sat. aq. sol. of $NaHCO_3$ (50 ml) and brine (50 ml), and dried over $MgSO_4$. All volatiles were removed under reduced pressure to obtain a crude product, which was purified by column chromatograph (SiO_2, CH_2Cl_2:acetone = 5:1, R_f= 0.42) to give pure product as a colorless oil (125 mg, 0.18 mmol, 86%); ^{1}H (300 MHz, $CDCl_3$) δ 0.73-0.75 (d, *J*= 6.6 Hz, 3H), 1.41-1.69 (m, 20H), 1.77-1.87 (m, 2H), 1.90-1.97 (m, 2H), 3.06-3.10 (d, *J*= 11.4, 1H), 3.64-3.73 (m, 5H), 3.84-4.20 (m, 5H), 6.00-6.03 (d, *J*= 7.7 Hz, 1H), 6.26-6.36 (m, 2H), 6.82-6.85 (d, *J*= 8.1 Hz, 1H), 6.96-7.01 (m, 1H), 7.07-7.12 (m, 1H), 7.18-7.21 (d, *J*= 7.7 Hz, 1H), 7.29-7.35 (m, 2H), 7.49-7.58 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1 (q), 25.7 (t), 25.8 (t), 25.9 (t), 26.0 (t), 29.1 (t), 29.2



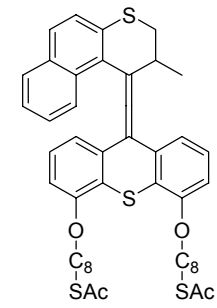
(t), 29.4 (t), 31.7 (d), 32.7 (t), 37.2 (t), 62.9 (t), 68.9 (t), 69.0 (t), 109.2 (d), 109.3 (d), 119.7 (d), 121.6 (d), 123.6 (s), 124.2 (d), 124.5 (d), 124.9 (s), 125.33 (d), 125.36 (d), 125.39 (d), 126.2 (d), 127.3 (d), 127.4 (d), 130.8 (s), 131.2 (s), 131.6 (s), 132.3 (s), 134.6 (s), 135.9 (s), 136.2 (s), 138.6 (s), 154.6 (s), 155.5 (s), due to overlap of the carbon absorptions, the signals in the tails of the molecule, 5 (t) were not observed; *m/z* (DEI, %) = 696 (M^+, 100); HRMS (EI): calcd. for $C_{43}H_{52}O_4S_2$: 696.3307, found 696.3276.

4,5-Bis({8-[(*p*-tosyl)oxy]octyl}oxy)-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.29)



To a mixture of **6.28** (43 mg, 0.062 mmol) and pyridine (0.022 mL, 0.271 mmol) in $CHCl_3$ (5 mL) was added tosyl chloride (26 mg, 0.136 mmol) at 0ºC. The mixture was stirred and the reaction was followed by TLC. If starting material or monotosylated product was detected, more tosyl chloride was added to the reaction mixture. After stirring for 72h, the reaction mixture was quenched with water (20 ml) and was subsequently extracted with ethyl acetate (3x 10 ml). The combined organic layers were washed with an aq. sol. of 10% HCl (10 ml), water (10 ml), sat. aq. sol. $NaHCO_3$ (10 ml), water (10 ml) and brine (10 ml), and dried over $MgSO_4$. The solvents were evaporated under reduced pressure to obtain the crude product. This crude product was purified by column chromatography (SiO_2, hexane:ethyl acetate = 3:1, R_f= 0.33) to give pure ditosylate as a colorless oil (52 mg, 0.052 mmol, 83%); ^{1}H (300 MHz, $CDCl_3$) δ 0.72-0.74 (d, *J*= 6.6 Hz, 3H), 1.23-1.95 (m, 24H), 2.41 (s, 3H), 2.42 (s, 3H), 3.05-3.09 (m, 1H), 3.67-3.73 (m, 1H), 3.82-4.18 (m, 9H); 6.01-6.03 (d, *J*= 7.2 Hz, 1H), 6.25-6.36 (m, 2H), 6.82-6.84 (d, *J*= 8.1 Hz, 1H), 6.94-6.99 (m, 1H), 7.06-7.10 (m, 1H), 7.18-7.20 (d, *J*= 7.8 Hz, 1H), 7.26-7.36 (m, 6H), 7.48-7.59 (m, 3H), 7.78-7.80 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 19.0 (q), 21.6 (q), 25.3 (t), 25.8 (t), 25.9 (t), 28.79 (t), 28.54 (t), 28.87 (t), 28.95 (t), 29.06 (t), 29.11 (t), 31.7 (d), 37.2 (t), 68.8 (t), 68.9 (t), 70.6 (t), 109.1 (d), 109.3 (d), 119.7 (d), 121.6 (d), 123.6 (s), 124.2 (d), 124.5 (d), 124.8 (s), 125.3 (2xd), 125.4 (d), 126.3 (d), 127.3 (d), 127.4 (d), 130.7(s), 131.2 (s), 131.5 (s), 132.2 (s), 133.1 (s), 134.6 (s), 135.9 (s), 136.2 (s), 138.6 (s), 144.6 (s), 154.5 (s), 155.5 (s); due to overlap the following were not observed: 1xq, 4xd, 4xt, 2xs; MS (electro-spray) 1027.5 (M+23(Na)).

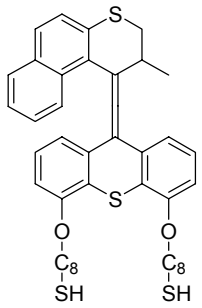
4,5-Bis{[8-(acetylsulfanyl)octyl]oxy}-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.30)



A mixture of ditosylate **6.29** (44 mg, 0.044 mmol) and potassium thioacetate (0.29 mmol, 33 mg) in DMF (or acetone, 5 mL) was stirred overnight at room temperature. The reaction was quenched by adding water (30 ml) and stirring for 30 min. The water layer was extracted with CH_2Cl_2 (3x 15 ml) and the combined organic layers were washed with water (25 ml) and brine (25 ml), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the crude product, which was purified by column chromatography (SiO_2, hexane:ethyl acetate = 4:1, R_f=0.40) to obtain the pure dithioacetate as a yellow oil (34 mg, 0.042 mmol, 95%); ^{1}H (300 MHz, $CDCl_3$) δ 0.73-0.75 (d, *J*= 7.0 Hz, 3H), 1.20-1.65 (m, 20H), 1.76-1.83 (m, 2H), 1.88-1.95 (m, 2H), 2.32 (s, 3H), 2.33 (s, 3H), 2.86-2.90 (m, 4H), 3.05-3.09 (dd, *J*= 11.4, 2.9 Hz, 1H), 3.67-3.73 (dd, *J*= 11.4, 7.3, 1H), 3.85-4.20 (m, 5H), 6.00-6.02 (d, *J*= 7.3 Hz, 1H), 6.25-6.36 (m, 2H), 6.82-6.85 (d, *J*= 8.1 Hz, 1H), 6.95-7.00 (m, 1H), 7.07-7.12 (m, 1H),

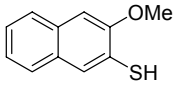
7.18-7.21 (d, *J*= 7.3 Hz, 1H), 7.26-7.31 (m, 1H), 7.33-7.36 (d, *J*= 8.4 Hz, 1H), 7.49-7.58 (m, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 19.1 (q), 25.9 (t), 26.1 (t), 26.1 (t), 26.2 (t), 28.8 (t), 29.1 (t), 29.16 (t), 29.22 (t), 29.5 (t), 29.7 (t), 29.8 (t), 30.6 (q), 31.8 (d), 37.2 (t), 68.9 (t), 69.0 (t), 109.2 (d), 109.4 (d), 119.7 (d), 121.7 (d), 123.7 (s), 124.2 (d), 124.6 (d), 125.0 (s), 125.4 (d), 126.2 (d), 127.3 (d), 127.4 (d), 130.8 (s), 131.3 (s), 131.7 (s), 132.4 (s), 134.7 (s), 135.9 (s), 136.3 (s), 138.6 (s), 154.6 (s), 155.6 (s), 196.0 (s), 7 signals could not be observed individually; a mass spectrum of this product could not be obtained; The enantiomers of dithioacetate **6.30** were resolved by preparative chiral HPLC employing a Chiralcel AD column as the stationary phase and a mixture of *n*-heptane : *i*-propanol 49 : 1 as the eluent (1 ml·min^{-1}). The elution time of the first fraction was *t*= 12.7 min and the elution time of the second fraction was *t*= 14.9 min. The synthesis towards the functionalized gold nanoparticles **6.1** was further performed with the second eluted fraction, which by CD spectroscopy was assigned to be (2'*S*)-(*P*)-**6.30**.

4,5-Bis[(8-sulfanyloctyl)oxy]-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-b]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.31)



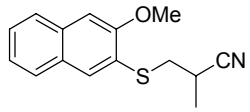
To the solution of dithioacetate **6.30** (32 mg, 0.039 mmol) in THF (2 mL) and methanol (2 mL) was added sodium methoxide (0.094 mmol, 5 mg). The reaction mixture was stirred for 2h at room temperature. The reaction was quenched with a sat. aq. sol of NH_4Cl. The water layer was extracted with ethyl acetate (twice) and the combined organic layers were washed with water and brine, and dried over $MgSO_4$. The solvent was evaporated under the reduced pressure to obtain dithiol (23 mg, 0.032 mmol, 81%). No further purification was performed to avoid oxidation of the sensitive thiol moieties and the material was directly used the subsequent reaction; ^{1}H (300 MHz, $CDCl_3$) δ 0.73-0.75 (d, *J* = 7.0 Hz, 3H), 1.20-1.65 (m, 20H), 1.87-2.00 (m, 4H), 2.50-2.58 (m, 4H), 3.05-3.10 (dd, *J*= 11.4, 2.6 Hz, 1H), 3.70-3.74 (dd, *J*= 11.4, 7.3 Hz, 1H), 3.90-4.20 (m, 5H), 6.00-6.03 (dd, *J*= 7.7, 1.1 Hz, 1H), 6.26-6.36 (m, 2H), 6.82-6.85 (d, *J*= 7.7 Hz, 1H), 6.96-7.01 (m, 1H), 7.07-7.12 (m, 1H), 7.19-7.21 (d, *J*= 7.5 Hz, 1H), 7.26-7.32 (m, 1H), 7.33-7.36 (d, *J*= 8.4 Hz, 1H), 7.49-7.59 (m, 3H), the two thiol protons could not be assigned.

3-Methoxy-naphthalene-2-thiol (6.33)



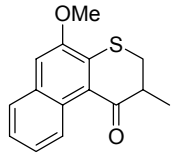
To a solution of 2-methoxynaphthalene **6.32** (22.2 g, 0.14 mol) in THF (300 ml) was added at 0°C dropwise *n*-BuLi (92 ml, 0.15 mol). After stirring for 1h at 0°C, the yellow solution was cooled to -80°C and elemental sulfur (S_8) was added (4.8 g, 19 mmol). After allowing the mixture reach room temperature overnight, the remaining organometallics were quenched with a sat. sol. of aq. NH_4Cl (500 ml) followed by extraction with ether (2x 300 ml). The combined organic layers were washed with brine (2x 500 ml), dried ($MgSO_4$) and all volatiles were removed under reduced pressure yielding the desired thionaphthol **6.33** as a slightly yellow solid (24.7 g, 0.13 mol, 93%) together with a small amount (<5%) of the isomeric 2-methoxy-naphthalene-1-thiol. The mixture of the isomers was immediately used in the subsequent reaction; ^{1}H (300 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.12 (d, 1H), 7.33-7.39 (m, 2H), 7.63-7.71 (m, 2H), 7.76 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 55.7 (q), 105.2 (d), 122.6 (s), 124.0 (d), 125.4 (d), 126.1 (d), 126.4 (d), 127.1 (d), 128.8 (s), 132.5 (s) 153.0 (s); *m/z* (EI, %) = 190 (M^+, 100); HRMS(EI): calcd. for $C_{11}H_{10}OS$: 190.0452, found: 190.0451.

3-(3-Methoxy-naphthalen-2-ylsulfanyl)-2-methyl-propionitrile (6.34)



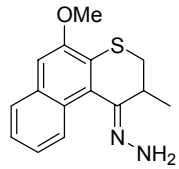
Methacrylonitrile (25 ml) was cooled to -20°C and Triton B (0.2 ml) was added. Stirring of the mixture was continued for 15 min at this temperature and then thiol **6.33** was added (1.7 g, 8.9 mmol). The temperature was allowed to reach room temperature and was then heated at reflux overnight. After cooling to room temperature, a sat. sol. of aq. NH_4Cl (100 ml) was added and the reaction mixture was extracted with ether (2x 75 ml). The yellow oil obtained after drying of the organic layers ($MgSO_4$) and removal of all volatiles under reduced pressure was purified by column chromatography (SiO_2, heptane:ethyl acetate, R_f= 0.21) and recrystallized from a mixture of heptane and ethyl acetate to yield a white powder which consisted of a single isomer of **6.34** (1.3 g, 5.1 mmol, 57%); m.p. 91.8-93.2°C; ^{1}H (300 MHz, $CDCl_3$) δ 1.44-1.46 (d, *J*= 7.0 Hz, 3H), 2.75-2.82 (m, 1H), 3.02-3.09 (dd, *J*= 13.5, 7.7 Hz, 1H), 3.25-3.32 (dd, 13.5, 7.0 Hz, 1H), 4.02 (s, 3H), 7.15 (s, 1H), 7.35-7.40 (m, 1H), 7.43-7.48 (m, 1H), 7.71-7.74 (m, 2H), 7.83 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 17.1 (q), 25.6 (d), 35.6 (t), 55.6 (q), 105.5 (d), 121.4 (s), 123.5 (s), 124.0 (d), 126.1 (d), 126.3 (d), 126.7 (d), 128.4 (s), 130.3 (d), 133.4 (s), 155.4 (s); *m/z* (EI, %) = 257 (M^+, 100), 203 (84); HRMS(EI): calcd. for $C_{15}H_{15}NOS$: 257.0874, found: 257.0872; ele. anal., calc. (%): C, 70.0; H, 5.87; N, 5.44; S, 12.46; found (%): C, 70.4; H, 6.90; N, 5.22; S, 13.30.

2,3-Dihydro-5-methoxy-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1-one (6.35)



Nitrile **6.34** (1.0 g, 3.9 mmol) was added to stirred PPA (20 ml) at 60°C whereupon the temperature was raised to 110°C for 3h. The reaction mixture was poured on ice (100 g) and allowed to hydrolyze overnight. The reaction mixture was extracted with ether (3x 50 ml) and the combined organic layers were washed with brine (2x 100 ml), dried ($MgSO_4$) and subsequently removed under reduced pressure giving a brown oil. This oil was purified by column chromatography (SiO_2, heptane:ethyl acetate= 16:1, R_f= 0.33) yielding the desired ketone **6.35** as a colorless oil (0.63 g, 2.4 mmol, 63%) which solidified upon standing; 57.4-59.5°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37-1.39 (d, *J*= 6.2 Hz, 3H), 3.09-3.26 (m, 3H), 4.02 (s, 3H), 7.19 (s, 1H), 7.39-7.47 (m, 2H), 7.66-7.69 (dd, *J*= 9.2, 0.8 Hz, 1H), 8.94-8.97 (d, *J*= 7.7 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 14.8 (q), 31.4 (t), 41.8 (d), 55.8 (q), 109.3 (d), 125.1 (d), 125.4 (d), 125.9 (d), 126.3 (s), 126.8 (d), 127.4 (s), 131.5 (s), 137.4 (s), 151.9 (s), 199.0 (s); *m/z* (EI, %) = 258 (M^+, 76), 216 (100); HRMS(EI): calcd. for $C_{15}H_{14}O_2S$: 258.0714, found: 258.0718.

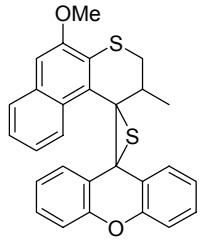
2,3-Dihydro-5-methoxy-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1-one hydrazone (6.36)



A mixture of ketone **6.35** (220 mg, 0.85 mmol), hydrazine monohydrate (5 ml) and ethanol (5 ml) was heated at reflux overnight. After cooling, ethyl acetate (50 ml) and water (100 ml) were added to the reaction mixture. The water layer was extracted with ethyl acetate (50 ml) and the combined organic layers were washed with water (100 ml) and brine (2x 100 ml). Drying over Na_2SO_4 and subsequent removal of all volatiles under reduced pressure gave a yellowish solid. This solid was precipitated from a small amount of ethyl acetate from which the desired hydrazone **6.36** could be collected as small white crystals (140 mg, 0.51 mmol, 61%); m.p. 228.5-228.6°C; ^{1}H (300 MHz, $CDCl_3$) δ 1.30-1.32 (d, *J*= 6.6 Hz, 3H), 2.65-2.73 (dd, *J*= 12.8, 11.2 Hz, 1H), 3.17-3.23 (dd, *J*= 12.8, 5.5 Hz, 1H), 3.47-3.57 (m, 1H), 3.99 (s, 3H), 5.58 (br s,

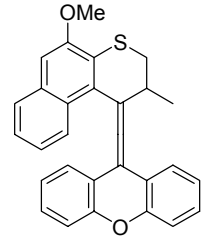
2H), 7.06 (s, 1H), 7.32-7.41 (m, 2H), 7.67-7.70 (m, 1H), 8.32-8.36 (m, 1H); ^{13}C (50 MHz, $CDCl_3$) δ 14.7 (q), 33.1 (d), 35.7 (t), 56.0 (q), 105.1 (d), 124.4 (d), 125.7 (d), 125.8 (d), 126.9 (d), 127.7 (s), 128.7 (s), 131.8 (s), 133.4 (s), 149.4 (s), 153.2 (s); *m/z* (EI, %) = 272 (M^+, 100); HRMS(EI): calcd. for $C_{15}H_{16}N_2OS$: 272.0983, found: 272.0985.

Dispiro[2,3-dihydro-5-methoxy-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1,2'-thiirane-3',9''-(9''*H*-xanthene)] (6.39)



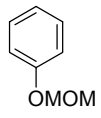
This compound was prepared according to the procedure described above for **6.23** from hydrazone **6.36** (120 mg, 0.44 mmol) and thioketone **6.38** (92 mg, 0.43 mmol). After column chromatography (SiO_2, heptane: ethyl acetate= 16:1, R_f= 0.37) the episulfide **6.39** was obtained as a white solid as a mixture of two isomers (170 mg, 0.37 mmol, 87%); *m/z* (EI, %) = 454 (M^+, 100); HRMS(EI): calcd. for $C_{28}H_{22}O_2S_2$: 454.1061, found: 454.1048.

9-(2,3-Dihydro-5-methoxy-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1-ylidene)-9*H*-xanthene (6.40)



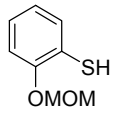
A solution of episulfide **6.39** (0.42 g, 0.93 mmol) was heated at reflux in *p*-xylene (10 ml) in presence of copper powder (200 mg, 3.1 mmol) overnight. The *p*-xylene was removed under reduced pressure and the remaining oil was purified by column chromatography (SiO_2, heptane: ethyl acetate = 50:1, R_f= 0.25) after which the desired alkene was obtained as a white solid (0.33 g, 0.78 mmol, 85%); m.p. >260°C; ^{1}H (300 MHz, $CDCl_3$) δ 0.79-0.82 (d, *J*= 7.0 Hz, 3H), 3.19-3.22 (d, *J*= 10.6 Hz, 1H), 3.76-3.82 (dd, *J*= 10.6, 6.6 Hz, 1H), 4.06 (s, 3H), 4.25-4.30 (m, 1H), 6.23-6.25 (m, 2H), 6.81-6.86 (m, 2H), 7.03-7.12 (m, 3H), 7.22-7.39 (m, 4H), 7.52-7.54 (d, *J*= 8.1 Hz, 1H), 7.57-7.60 (d, *J*= 7.7 Hz, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 18.0 (q), 30.0 (d), 36.6 (t), 55.8 (q), 104.4 (d), 115.8 (d), 116.9 (d), 122.2 (d), 123.0 (d), 123.4 (s), 123.5 (d), 123.9 (d), 124.7 (d), 125.1 (s), 125.9 (s), 126.2 (s), 126.4 (d), 126.7 (d), 127.4 (s), 127.5 (d), 128.18 (d), 128.22 (d), 131.86 (s), 131.91 (s), 134.2 (s), 153.46 (s), 153.53 (s), 154.9 (s); *m/z* (EI, %) = 422 (M^+, 100); HRMS(EI): calcd. for $C_{28}H_{22}O_2S$: 422.1340, found: 422.1343.

Methoxymethoxybenzene (6.42)



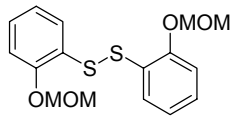
To a suspension of NaH (6.0 g, 0.25 mol) in THF (100 ml) was added at 0°C phenol (9.4 g, 0.10 mol). When the evolution of hydrogen had ceased, MOMCl (5.0 ml, 65 mmol) was added and the reaction mixture was stirred overnight. The excess NaH was quenched with a sat. sol. of NH_4Cl (200 ml) followed by extraction with ether (3x 50 ml). The organic layers were then washed with an aq. sol. of 1*N* NaOH (3x 100 ml) and dried (Na_2SO_4). After removal of the organic solvents, the desired product was obtained as a colorless liquid (7.5 g, 54 mmol, 84%); ^{1}H (400 MHz, $CDCl_3$) δ 3.49 (s, 3H), 5.19 (s, 2H), 6.99-7.06 (m, 3H), 7.28-7.32 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 55.6 (q), 94.1 (t), 116.0 (d), 121.6 (d), 129.3 (d), 157.1 (s); *m/z* (EI, %) = 138 (M^+, 100); HRMS (EI): calcd. for $C_8H_{10}O_2$: 138.0681, found 138.0696.

2-Methoxymethoxybenzenethiol (6.43)



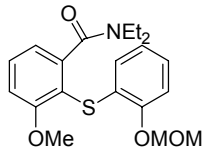
To a solution of **6.42** (6.9 g, 50 mmol) in THF (150 ml) at 0°C was added dropwise *n*-BuLi (33 ml, 53 mmol). After stirring for 1h, the solution was cooled to -80°C and elemental sulfur (S_8, 1.76 g, 6.9 mmol) was added. The reaction was then allowed to reach room temperature overnight and a sat. sol. of NH_4Cl (200 ml) was added. Extraction with ether (2x 100 ml), drying (Na_2SO_4) and evaporation of the volatiles gave thiophenol **6.43** (6.7 g, 39 mmol, 79%) as a yellow liquid containing some impurities. The product was not further purified but directly used in the next step; ^{1}H (400 MHz, $CDCl_3$) δ 3.51 (s, 3H), 5.25 (s, 2H), 6.88-7.27 (m, 4H); ^{13}C (100 MHz, $CDCl_3$) δ 56.0 (q), 94.6 (t), 114.4 (d), 121.5 (s), 122.1 (d), 126.1 (d), 129.2 (d), 152.4 (s); *m/z* (EI, %) = 170 (M^+, 100); HRMS (EI): calcd. for $C_8H_{10}O_2S$: 170.0401, found 170.0397.

Di(2-methoxymethoxyphenyl)disulfide (6.44)



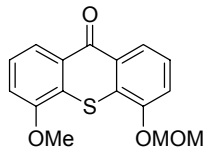
Following a literature procedure,[13] a mixture of $CuSO_4 \cdot 5\ H_2O$ (7.5 g, 30 mmol), $KMnO_4$ (7.5 g, 48 mmol), tetraoctylammonium bromide (0.5 g, 0.9 mmol) and thiol **6.43** (6.7 g, 39 mmol) in CH_2Cl_2 (200 ml) was stirred for 3h at room temperature. The solids were removed by filtration over celite and the desired compound was subsequently obtained pure by flash column chromatography as a yellow liquid (4.2 g, 12.4 mmol, 63%); ^{1}H (400 MHz, $CDCl_3$) δ 3.52 (s, 6H), 5.25 (s, 4H), 6.95-6.99 (m, 2H), 7.08-7.10 (dd, *J*= 8.2, 1.3 Hz, 2H), 7.14-7.19 (m, 2H), 7.53-7.56 (dd, *J*= 7.9, 1.7 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) δ 56.3 (q), 94.8 (t), 114.4 (d), 122.5 (d), 125.6 (s), 127.5 (d), 127.7 (d), 154.2 (s); *m/z* (EI, %) = 338 (M^+, 66), 138 (100); HRMS (EI): calcd. for $C_{16}H_{18}O_4S_2$: 338.0646, found 338.0646.

***N*,*N*-Diethyl-3-methoxy-2-(2-methoxymethoxy-phenylsulfanyl)-benzamide (6.45)**



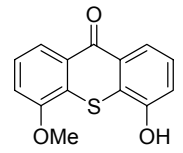
Following the procedure previously used for the synthesis of **6.19** and **6.20**, to a solution of a complex of *s*-BuLi (11.3 ml, 14.6 mmol) and TMEDA (2.2 ml, 14.6 mmol) in THF (100 ml) at -80°C was added disulfide **6.44** (3.95 g, 11.7 mmol) in THF (20ml). The reaction was stirred overnight while allowing the temperature to reach room temperature. Quenching with a sat. sol. of NH_4Cl (200 ml), extraction with ether (3x 100 ml), washing of the organic layers with brine (200 ml), gave after drying ($MgSO_4$) and evaporation of the organic volatiles a brown oil which was purified by column chromatography (SiO_2, heptane:ethyl acetate= 1:1, R_f= 0.3) amide **6.45** as a slightly yellow oil (2.30 g, 6.1 mmol, 52%); ^{1}H (300 MHz, $CDCl_3$) δ 0.95-1.00 (t, *J*= 7.0 Hz, 3H), 1.16-1.21 (t, *J*= 7.0 Hz, 3H), 2.96-3.15 (m, 2H), 3.25-3.37 (m, 1H), 3.51 (s, 3H), 3.67-3.82 (m, 1H), 3.76 (s, 3H), 5.23 (s, 2H), 6.68-6.71 (d, *J*= 7.7 Hz, 1H), 6.76-6.81 (m, 1H), 6.93-6.96 (m, 2H), 6.99-7.06 (m, 2H), 7.41-7.47 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 12.2 (q), 13.6 (q), 38.2 (t), 42.4 (t), 55.8 (2xq), 94.7 (t), 111.0 (d), 114.3 (d), 115.6 (s), 118.4 (d), 122.0 (d), 125.5 (d), 126.4 (s), 126.7 (d), 131.0 (d), 144.9 (s), 153.0 (s), 160.3 (s), 168.4 (s); *m/z* (EI, %) = 375 (M^+, 100), 259 (48); HRMS (EI): calcd. for $C_{20}H_{25}NO_4S$: 375.1504, found 375.1491.

4-Methoxy-5-methoxymethoxy-9*H*-thioxanthen-9-one (6.46)



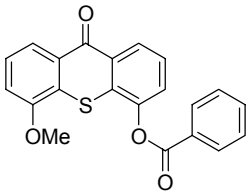
Following the procedure for the synthesis of ketone **6.16**, amide **6.45** (1.15 g, 3.07 mmol) treated with freshly prepared LDA (12 mmol) in THF (70 ml) at 0°C. After workup and purification by column chromatography (SiO_2, heptane:ethyl acetate=2:1, R_f= 0.50) the ketone **6.46** (0.69 g, 2.28 mmol, 75%) was obtained as a yellowish solid; m.p. 137.0-138.3°C; ^{1}H (300 MHz, $CDCl_3$) δ 3.57 (s, 3H), 4.06 (s, 3H), 5.40 (s, 2H), 7.14-7.16 (d, *J*= 8.1 Hz, 1H), 7.42-7.48 (m, 3H), 8.24-8.32 (m, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 56.1 (q), 56.3 (q), 94.9 (t), 111.8 (d), 115.9 (d), 121.1 (d), 122.3 (d), 125.7 (2xd), 127.2 (s), 128.1 (s), 129.6 (s), 129.7 (s), 152.2 (s), 154.5 (s), 179.7 (s); *m/z* (EI, %) = 302 (M^+, 100); HRMS (EI): calcd. for $C_{16}H_{14}O_4S$: 302.0613, found 302.0613.

4-Hydroxy-5-methoxy-thioxanthen-9*H*-one (6.47)



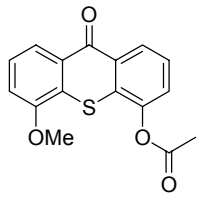
A mixture of thioxanthon **6.46** (0.39 g, 1.29 mmol), THF (40 ml) and an aq. sol. of 12*N* HCl (20 ml) was stirred overnight at room temperature. To the yellow solution was then added water (150 ml) followed by extraction with chloroform (3x 100 ml). After drying (Na_2SO_4) and evaporation of the organic volatiles, **6.47** was obtained as a hardly soluble yellow solid which was sufficiently pure for further manipulations (0.30 g, 1.16 mmol, 90%); ^{1}H (400 MHz, DMSO-d_6) δ 4.03 (s, 3H), 7.21-7.23 (d, *J*= 7.7 Hz, 1H), 7.39-7.44 (m, 2H), 7.51-7.55 (s, 1H), 7.93-7.95 (d, *J*= 8.1 Hz, 1H), 8.04-8.07 (d, *J*= 8.1 Hz, 1H); ^{13}C (50 MHz, DMSO-d_6) δ 56.7 (q), 113.0 (d), 116.6 (d), 119.2 (d), 120.5 (d), 124.9 (s), 126.4 (d), 126.5 (d), 129.0 (s), 129.2 (s), 153.1 (2xs), 154.5 (s), 179.1 (s); *m/z* (EI, %) = 258 (M^+, 100), 243 (38); HRMS (EI): calcd. for $C_{14}H_{10}O_3S$: 258.0351, found 258.0354.

Benzoic acid 5-methoxy-9-oxo-9*H*-thioxanthen-4-yl ester (6.48)



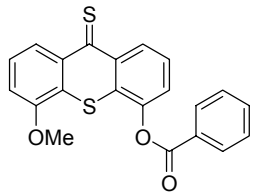
The phenol **6.47** (0.17 g, 0.66 mmol) was dissolved in $CHCl_3$ (50 ml) and benzoyl chloride (1.0 ml, 8.5 mmol) and triethylamine (1.0 ml, 7.2 mmol) were added. The mixture was then stirred overnight and ether (100 ml) was added. The organic layers were washed with an aq. sol. of 1*N* HCl (2x 100 ml), an aq. sol. of 2*N* NaOH (2x 100 ml), dried (Na_2SO_4) and then all organic volatiles including the excess benzoyl chloride were removed under reduced pressure. The yellow solid obtained was purified by column chromatography (SiO_2, heptane:ethyl acetate = 4:1, R_f= 0.29) and then by recrystallization from ethanol giving fine, slightly yellow needles (0.12 g, 0.33 mmol, 50%); m.p. 224.8-225.5°C; ^{1}H (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.13-7.15 (dd, *J*= 8.1, 1.1 Hz, 1H), 7.45-7.49 (t, *J*= 8.1 Hz, 1H), 7.55-7.63 (m, 4H), 7.72-7.74 (m, 1H), 8.25-8.27 (dd, *J*= 8.2, 1.3 Hz, 1H), 8.34-8.37 (m, 2H), 8.57-8.59 (dd, *J*= 7.7, 1.8 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 56.3 (q), 112.4 (d), 121.5 (d), 125.7 (d), 125.9 (d), 126.3 (d) 126.4 (s), 127.1 (d), 128.6 (s), 128.8 (d), 129.7 (s), 130.3 (s), 130.5 (d), 131.2 (s), 134.1 (d), 146.3 (s), 154.5 (s), 164.2 (s), 179.6 (s); *m/z* (EI, %) = 362 (M^+, 42), 105 (100); HRMS (EI): calcd. for $C_{21}H_{14}O_4S$: 362.0613, found 362.0603; ele. anal., calc. (%): C, 69.6; H, 3.89; S, 8.85; found (%): C, 69.1; H, 3.82; S, 9.02.

Acetic acid 5-methoxy-9-oxo-9*H*-thioxanthen-4-yl ester (6.49)



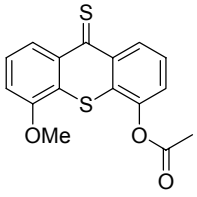
The phenol **6.47** (0.30 g, 1.16 mmol) was dissolved in $CHCl_3$ (50 ml) and acetyl chloride (2.0 ml, 28 mmol) and triethylamine (2.0 ml, 14 mmol) were added. The mixture was then stirred overnight and ether (100 ml) was added. The organic layers were washed with an aq. sol. of 1*N* HCl (2x 100 ml), an aq. sol. of 2*N* NaOH (2x 100 ml), dried (Na_2SO_4) and then all organic volatiles were removed under reduced pressure. The yellow solid obtained was purified by recrystallization from ethanol giving fine slightly beige needles (0.27 g, 0.90 mmol, 78%); m.p. 191.6-191.9°C; ^{1}H (400 MHz, $CDCl_3$) δ 2.49 (s, 3H), 4.05 (s, 3H), 7.15-7.17 (dd, *J*= 7.9, 0.9 Hz, 1H), 7.45-7.54 (m, 3H), 8.23-8.25 (dd, *J*= 8.1, 1.1 Hz, 1H), 8.52-8.54 (dd, *J*= 7.9, 1.6 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 20.9 (q), 56.4 (q), 112.4 (d), 121.5 (d), 125.6 (d), 125.8 (d), 126.2 (s), 126.3 (d), 127.0 (d), 129.7 (s), 130.3 (s), 130.8 (s), 146.1 (s), 154.5 (s), 168.5 (s), 179.5 (s); *m/z* (EI, %) = 300 (M^+, 32), 258 (100); HRMS (EI): calcd. for $C_{16}H_{12}O_4S$: 300.0456, found 300.0458; ele. anal., calc. (%): C, 63.99; H, 4.03; S, 10.68; found (%): C, 63.9; H, 4.10; S, 11.06.

Benzoic acid 5-methoxy-9-thioxo-9*H*-thioxanthen-4-yl ester (6.50)



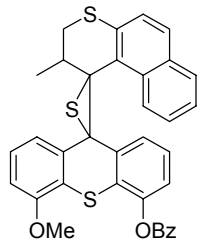
Compound **6.50** was synthesized following the procedure for **6.51**. Starting from ketone **6.48** (110 mg, 0.30 mmol), the desired thioketone **6.50** was obtained after flash column chromatography (SiO_2, heptane: ethyl acetate=8:1, R_f=0.32) as a brown/green solid (100 mg, 0.26 mmol, 87%); ^{1}H (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.10-7.12 (d, *J*= 7.7 Hz, 1H), 7.37-7.75 (m, 6H), 8.33-8.36 (m, 2H), 8.61-8.63 (d, *J*= 8.4 Hz, 1H), 8.93-8.95 (dd, *J*= 8.2, 1.2 Hz, 1H); due to the low soluabilty and limited stability of the compound, no ^{13}C analysis could be performed; *m/z* (EI, %) = 378 (M^+, 35), 362 (8), 105 (100); HRMS (EI): calcd. for $C_{21}H_{14}O_3S_2$: 378.0384, found 378.0392.

Acetic acid 5-methoxy-9-thioxo-9*H*-thioxanthen-4-yl ester (6.51)



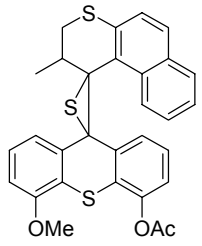
A suspension of ketone **6.49** (140 mg, 0.46 mmol) in toluene (10 ml) was heated to reflux in presence of P_4S_{10} (250 mg, 0.56 mmol). After 30 min the mixture turned dark green and was filtered to remove the solid residues. These were washed with CH_2Cl_2 and all organic volatiles were removed under reduced pressure. The resulting brown residue was purified by column chromatography (SiO_2, heptane:ethyl acetate=4:1, R_f=0.30) and was obtained as a light green solid (90 mg, 0.28 mmol, 62%); ^{1}H (400 MHz, $CDCl_3$) δ 2.50 (s, 3H), 4.05 (s, 3H), 7.13-7.15 (dd, *J*= 8.1, 1.1 Hz, 1H), 7.38-7.46 (m, 3H), 8.59-8.61 (dd, *J*= 8.4, 1.1 Hz, 1H), 8.88-8.90 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 20.9 (q), 56.5 (q), 111.5 (d), 121.5 (s), 124.7 (d), 125.2 (d), 125.9 (s), 126.2 (d), 126.7 (d), 130.6 (d), 138.2 (s), 138.6 (s), 146.2 (s), 154.6 (s), 168.5 (s), 210.6 (s); *m/z* (EI, %) = 316 (M^+, 45), 274 (100); HRMS (EI): calcd. for $C_{16}H_{12}O_3S_2$: 316.0228, found 316.0243.

Dispiro[2,3-dihydro-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1,2'-thiirane-3',9''-(4''-benzoyl-5''-methoxy-9''*H*-thioxanthene)] (6.52)



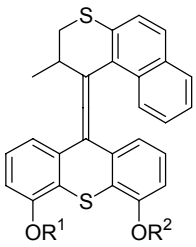
This compound was prepared according to the procedure used for **6.51**. Starting with hydrazone **6.3** (120 mg, 0.50 mmol) and thioketone **6.50** (100 mg, 0.26 mmol), the episulfide **6.52** was obtained as a mixture of two isomers as a white solid (110 mg, 0.19 mmol, 70%); ^{1}H (400 MHz, $CDCl_3$) δ 1.16-1.18 (d, *J*= 6.0 Hz, 3H), 1.17-1.19 (d, *J*= 6.0 Hz, 3H), 2.15-2.19 (dd, *J*= 11.9, 6.4 Hz, 1H), 2.22-2.26 (dd, *J*= 11.9, 5.3 Hz, 1H), 2.54-2.71 (m, 4H), 3.70 (s, 3H), 3.90 (s, 3H), 6.17-6.32 (m, 3H), 6.42-6.44 (d, *J*= 8.1 Hz, 1H), 6.63-6.65 (dd, *J*= 8.2, 1.3 Hz, 1H), 6.69-6.71 (dd, *J*= 7.7, 1.1 Hz, 1H), 6.86-6.88 (d, *J*= 8.1 Hz, 1H), 6.94-6.96 (d, *J*= 8.4 Hz, 1H), 7.09-7.11 (d, *J*= 8.4 Hz, 1H), 7.23-7.72 (m, 18H), 7.99-8.01 (dd, *J*= 7.9 Hz, 1H), 8.30-8.37 (m, 4H), 8.72-8.74 (d, *J*= 8.4 Hz, 1H), 8.79-8.81 (d, *J*= 8.8 Hz, 1H); *m/z* (EI, %) = 590 (M^+, 19), 558 (94), 105 (100); HRMS(EI): calcd. for $C_{35}H_{26}O_3S_3$: 590.1044, found: 590.1048.

Dispiro[2,3-dihydro-2-methyl-1*H*-naphtho[2,1-*b*]thiopyran-1,2'-thiirane-3',9''-(4''-acetyl-5''-methoxy-9''*H*-thioxanthene)] (6.53)



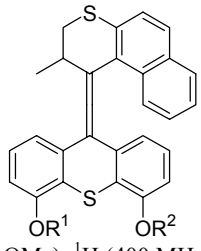
To a solution of hydrazone **6.3** (180 mg, 0.74 mmol) in CH_2Cl_2 (20 ml) were added Ag_2O (200 mg, 0.86 mmol), $MgSO_4$ (400 mg) and a sat. sol. of KOH in methanol (0.3 ml). After stirring for 60 min and the addition of additional portions of $MgSO_4$ (400 mg) and Ag_2O (200 mg), the suspension turned deep red and was filtered. To this was added a solution of the thioketone **6.51** (80 mg, 0.25 mmol) in cold CH_2Cl_2 (10 ml) and the reaction was stirred overnight. After evaporation of all volatiles, the crude episulfide was purified by column chromatography (SiO_2, heptane:ethyl acetate=8:1, R_f= 0.21) and obtained as a white solid as a 1:1 mixture of two isomers (100 mg, 0.19 mmol, 76%); ^{1}H (400 MHz, $CDCl_3$) δ 1.15-1.17 (d, *J*= 6.6 Hz, 3H), 1.19-1.20 (d, *J*= 6.6 Hz, 3H), 2.15-2.20 (dd, *J*= 11.5, 6.0 Hz, 1H), 2.21-2.25 (dd, *J*= 11.7, 5.1 Hz, 1H), 2.40 (s, 3H), 2.47 (s, 3H), 2.51-2.67 (m, 4H), 3.77 (s, 3H), 3.97 (s, 3H), 6.19-6.24 (m, 2H), 6.33-6.36 (dd, *J*= 8.1, 0.7 Hz, 1H), 6.46-6.48 (dd, *J*= 8.1, 1.1 Hz, 1H), 6.56-6.59 (dd, *J*= 8.1, 1.1 Hz, 1H), 6.62-6.65 (dd, *J*= 8.1, 1.5 Hz, 1H), 6.89-6.91 (dd, *J*= 8.1, 1.1 Hz, 1H), 6.97-6.99 (d, *J*= 8.4 Hz, 1H), 7.04-7.06 (d, *J*= 8.4 Hz, 1H), 7.14-7.17 (dd, *J*= 7.9, 1.3 Hz, 1H), 7.26-7.38 (m, 6H), 7.47-7.53 (m, 2H), 7.59-7.63 (m, 2H), 7.70-7.72 (dd, *J*= 8.1, 0.7 Hz, 1H), 7.95-7.98 (dd, *J*= 8.1, 1.1 Hz, 1H), 8.73-8.75 (d, *J*= 8.1 Hz, 1H), 8.81-8.83 (d, *J*= 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 20.8 (q), 20.9 (q), 21.0 (q), 21.1 (q), 34.7 (t), 35.8 (t), 40.5 (d), 40.9 (d), 56.1 (q), 56.2 (q), 61.3 (s), 61.4 (s), 65.2 (s), 65.6 (s), 108.3 (d), 108.9 (d), 120.0 (d), 121.1 (d), 121.7 (s), 122.1 (d), 123.1 (d), 123.2 (d), 123.9 (s), 124.0 (d), 124.09 (d), 124.11 (d), 124.2 (d), 124.7 (d), 125.07 (d), 125.09 (d), 125.2 (d), 125.5 (d), 125.6 (d), 126.0 (d), 126.66 (d), 126.74 (d), 126.86 (d), 126.96 (s), 127.1 (s), 127.9 (s), 128.1 (d), 128.2 (d), 128.8 (d), 130.0 (s), 131.59 (s), 131.61 (s), 132.00 (s), 132.03 (s), 132.2 (s), 132.4 (s), 134.5 (s), 134.6 (s), 139.6 (s), 140.8 (s), 145.4 (s), 146.2 (s), 153.8 (s), 154.7 (s), 168.7 (s), 168.9 (s); *m/z* (EI, %) = 528(M^+, 100), 496 (97), 486 (76); HRMS(EI): calcd. for $C_{30}H_{24}O_3S_3$: 528.0887, found: 528.0873.

Benzoic acid 5-methoxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1-ylidene)-9*H*-thioxanthen-4-yl ester (6.54)



A solution of episulfide **6.52** (110 mg, 0.186 mmol) was heated at reflux in *p*-xylene (10 ml) in presence of copper powder and triphenylphosphine (300 mg, 1.1 mmol) during 3d. After cooling to room temperature, the reaction mixture was filtered and all volatiles were removed under reduced pressure. The alkene **6.54** was obtained as a white solid (80 mg, 0.143 mmol after column chromatography (SiO_2, heptane:ethyl acetate= 16:1, R_f=0.20) as a mixture the *cis*- and *trans*-isomers (64 mg, 0.116 mmol, 62%); *trans*-**6.54** (R^1= OBz, R^2= OMe): ^{1}H (400 MHz, $CDCl_3$, ca. 96% isomerically pure) δ 0.79-0.80 (d, *J*= 7.0 Hz, 3H), 3.08-3.10 (dd, *J*= 11.0, 2.9, 1H), 3.69-3.75 (m, 1H), 3.73 (s, 3H), 4.12-4.15 (m, 1H), 6.03-6.06 (dd, *J*= 7.9, 0.9 Hz, 1H), 6.27-6.30 (dd, *J*= 8.1, 1.1 Hz, 1H), 6.37-6.40 (m, 1H), 6.95-6.99 (m, 1H), 7.07-7.11 (m, 1H), 7.25-7.73 (m, 11H), 8.36-8.38 (dd, *J*= 8.1, 1.1 Hz, 1H); *cis*-**6.54** (R^1= OMe, R^2= OBz): ^{1}H (400 MHz, $CDCl_3$, ca. 80% isomerically pure) δ 0.76-0.78 (d, *J*= 7.0 Hz, 3H), 3.05-3.09 (dd, *J*= 11.4, 2.9 Hz, 1H), 3.68-3.73 (dd, *J*= 11.4, 7.3 Hz, 1H), 3.91 (s, 3H), 4.10-4.14 (m, 1H), 6.31-6.33 (dd, *J*= 8.8, 1.1 Hz, 1H), 6.43-6.47 (m, 1H), 6.66-6.68 (dd, *J*= 7.9, 1.3 Hz, 1H), 6.84-6.86 (d, *J*= 8.1 Hz, 1H), 7.16-7.71 (m, 12H), 8.31-8.33 (dd, *J*= 8.8, 1.5 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$, mixture of *cis* and *trans* isomers) δ 19.2 (q), 19.3 (q), 32.0 (d), 32.2 (d), 37.0 (t), 37.1 (t), 56.02 (q), 56.06 (q), 108.1 (d), 108.7 (d), 119.5 (d), 120.1 (d), 120.4 (d), 121.8 (d), 122.0 (s), 123.6 (s), 124.26 (d), 124.34 (d), 124.41 (d), 124.52 (d), 124.84 (d), 124.90 (d), 125.34 (d), 125.49 (d), 125.61 (d), 125.97 (d), 126.24 (d), 126.51 (d), 126.80 (d), 127.39 (d), 127.43 (d), 127.47 (d), 127.56 (d), 127.87 (s), 128.40 (d), 128.48 (d), 128.53 (d), 128.64 (d), 129.19 (s), 129.38 (s), 129.48 (s), 130.47 (d), 130.54 (d), 130.63 (s), 130.70 (s), 131.15 (s), 131.24 (s), 131.29 (s), 131.70 (s), 131.76 (s), 133.53 (d), 133.59 (d), 133.76 (d), 134.77 (s), 134.79 (s), 136.83 (s), 136.92 (s), 136.99 (s), 137.56 (s), 139.0 (s), 147.0 (s), 147.8 (s), 155.2 (s), 156.1 (s), 164.2 (s), 164.5 (s); *m/z* (EI, %) = 558 (M^+, 100), 105 (63); HRMS(EI): calcd. for $C_{35}H_{26}O_3S_2$: 558.1323, found: 558.1318; The *cis* and *trans*-isomers of **6.54** could only be separated using chiral HPLC using an OD column as the stationary phase and a mixture of heptane and *i*-propanol as the eluent in a ratio of 98:2. The retention times of the four fractions were: t_1= 8.26 min, t_2= 9.28 min, t_3= 10.87 min and t_4= 19.00 min.

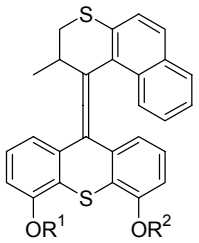
Acetic acid 5-methoxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1-ylidene)-9*H*-thioxanthen-4-yl ester (6.55)



A solution of episulfide **6.53** (100 mg, 0.19 mmol) and triphenylphosphine (200 mg, 0.76 mmol) in *p*-xylene (10 ml) was heated at reflux overnight. The solvent was removed followed by purified using column chromatography (SiO_2, heptane:ethyl acetate= 8:1, R_f= 0.22) giving the desired alkene (80 mg, 0.16 mmol, 85%) as a mixture of two isomers as a white solid. The least soluble isomer was obtained by precipitation from a mixture of heptane and ethyl acetate followed by recrystallization from chloroform as a white powder. The most soluble isomer was obtained 95% pure by evaporation of the mother liquor after recrystallization; Less soluble isomer; *trans*-**6.55** (R^1= OAc, R^2= OMe): ^{1}H (400 MHz, $CDCl_3$) δ 0.77-0.78 (d, *J*= 6.6 Hz, 3H), 2.49 (s, 3H), 3.07-3.10 (dd, *J*= 11.4, 2.9 Hz, 1H), 3.67-3.72 (dd, *J*= 11.4, 7.3 Hz, 1H), 3.78 (s, 3H), 4.07-4.11 (dqd, *J*= 7.3, 7.0, 2.9 Hz, 1H), 6.03-6.05 (dd, *J*= 7.7, 1.1 Hz, 1H), 6.29-6.31 (d, *J*= 8.1 Hz, 1H), 6.37-6.41 (m, 1H), 6.97-7.00 (m, 1H), 7.08-7.12 (m, 2H), 7.35-7.40 (m, 2H), 7.47-7.51 (m, 2H), 7.54-7.56 (d, *J*= 8.1 Hz, 1H), 7.57-7.60 (d, *J*= 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 19.2 (q), 21.0 (q), 32.0 (d), 37.1 (t), 56.2 (q), 108.1

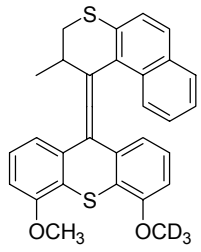
(d), 120.4 (d), 121.8 (d), 121.9 (s), 124.35 (d), 124.42 (d), 124.8 (d), 125.4 (d), 125.5 (d), 126.0 (d), 126.5 (d), 127.4 (d), 127.5 (d), 129.2 (s), 130.7 (s), 131.3 (2xs), 131.7 (s), 134.8 (s), 137.0 (s), 137.6 (s), 139.0 (s), 147.6 (s), 155.2 (s), 169.0 (s); More soluble isomer; *cis*-**6.55** (R^1= OMe, R^2= OAc): ^{1}H (400 MHz, $CDCl_3$) δ 0.75-0.77 (d, *J*= 7.0 Hz, 3H), 2.42 (s, 3H), 3.05-3.08 (dd, *J*= 11.4, 3.3 Hz, 1H), 3.67-3.72 (dd, *J*= 11.4, 7.3 Hz, 1H), 3.98 (s, 3H), 4.08-4.13 (m, 1H), 6.27-6.29 (dd, *J*= 7.9, 1.3 Hz, 1H), 6.39-6.43 (m, 1H), 6.52-6.54 (dd, *J*= 7.9, 1.3 Hz, 1H), 6.86-6.88 (dd, *J*= 8.1, 0.7 Hz, 1H), 7.10-7.16 (m, 2H), 7.22-7.40 (m, 3H), 7.47-7.56 (m, 2H), 7.58-7.60 (d, *J*= 8.4 Hz, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 19.2 (q), 20.9 (q), 32.1 (d), 37.0 (t), 56.1 (q), 108.7 (d), 119.4 (d), 120.0 (d), 123.5 (s), 124.2 (d), 124.4 (d), 125.3 (d), 125.6 (d), 126.2 (d), 126.4 (d), 126.8 (d), 127.4 (d), 127.5 (d), 130.6 (s), 131.1 (s), 131.3 (s), 131.7 (s), 134.8 (s), 136.8 (s), 137.0 (s), 139.7 (s), 146.8 (s), 156.1 (s), 168.6 (s); *m/z* (EI, %) = 496 (M^+, 100); HRMS(EI): calcd. for $C_{30}H_{24}O_3S_2$: 496.1167, found: 496.1175.

5-Methoxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1-ylidene)-9*H*-thioxanthen-4-ol (6.56)



To a solution of *cis*-**6.55** (20 mg, 44 μmol) in ether (2 ml) and methanol (2 ml) was added $NaBH_4$ (100 mg, 2.6 mmol) at room temperature. The mixture was stirred for 2h and another batch of $NaBH_4$ (100 mg, 2.6 mmol) was added. Stirring was continued for 2h and then the reaction mixture was quenched with a sat. sol. of aq. NH_4Cl (50 ml). The water layer was then extracted with CH_2Cl_2 (3x 50 ml), the combined organic layers were dried (Na_2SO_4) and then removed under reduced pressure giving a mixture of **6.55** and **6.56**. The mixture was separated by column chromatography (SiO_2, heptane:ethyl acetate=4:1, R_f= 0.18) giving the phenol *trans*-**6.56** as a white solid. *Trans*-**6.56** (R^1= OMe, R^2= OH), obtained from most soluble *cis*-**6.55**: ^{1}H (400 MHz, $CDCl_3$) δ 0.77-0.79 (d, *J*= 7.0 Hz, 3H), 3.03-3.07 (dd, *J*= 11.4, 3.3 Hz, 1H), 3.66-3.71 (dd, *J*= 11.4, 7.3 Hz, 1H), 4.00 (s, 3H), 4.09-4.13 (m, 1H), 5.99-6.01 (dd, *J*= 5.9, 3.3 Hz, 1H), 6.35-6.37 (m, 2H), 6.87-6.89 (d, *J*= 8.1 Hz, 1H), 7.05-7.15 (m, 2H), 7.20-7.26 (m, 1H), 7.34-7.38 (m, 2H), 7.55-7.61 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 19.2 (q), 32.3 (d), 37.1 (t), 56.1 (q), 108.6 (d), 112.5 (d), 120.1 (s), 120.3 (d), 121.4 (d), 123.2 (s), 124.42 (d), 124.46 (d), 125.4 (d), 125.7 (d), 126.6 (d), 127.2 (d), 127.48 (d), 127.51 (d), 130.9 (s), 131.35 (s), 131.37 (s), 132.5 (s), 134.8 (s), 136.7 (s), 138.0 (s), 140.4 (s), 151.7 (s), 156.2 (s); *Cis*-**6.56** (R^1= OH, R^2= OMe), obtained from most soluble *trans*-**6.55** according to the procedure given above for *trans*-**6.56**: ^{1}H (400 MHz, $CDCl_3$) δ 0.79-0.81 (d, *J*= 7.0 Hz, 3H), 3.05-3.09 (dd, *J*= 11.4, 2.9 Hz, 1H), 3.6-3.72 (dd, *J*= 11.4, 7.3 Hz, 1H), 3.81 (s, 3H), 4.18-4.22 (m, 1H), 6.04-6.06 (dd, *J*= 7.7, 1.1 Hz, 1H), 6.31-6.33 (dd, *J*= 8.2, 1.4 Hz, 1H), 6.40-6.44 (m, 1H), 6.91-6.94 (dd, *J*= 8.1, 1.1 Hz, 1H), 7.01-7.05 (m, 1H), 7.10-7.13 (m, 1H), 7.20-7.22 (dd, *J*= 7.7, 1.4 Hz, 1H), 7.27-7.31 (m, 1H), 7.35-7.38 (d, *J*= 8.4 Hz, 1H), 7.55-7.60 (m, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 19.2 (q), 32.2 (d), 37.1 (t), 56.1 (q), 108.0 (d), 113.5 (d), 119.9 (d), 121.7 (d), 121.9 (d), 124.3 (d), 124.4 (d), 125.4 (d), 125.5 (d), 126.4 (d), 127.5 (d), 127.6 (d), 130.8 (s), 131.3 (s), 132.6 (s), 134.9 (s), 136.8 (s), 138.4 (s), 140.3 (s), 152.9 (s), 155.3 (s), one (d) and two (s) signals were not observed; *m/z* (EI, %) = 454 (M^+, 100); HRMS(EI): calcd. for $C_{28}H_{22}O_2S_2$: 454.1061, 454.1063.

4-Methoxy(d_3)-5-methoxy-9-(2',3'-dihydro-2'-methyl-1'*H*-naphtho[2,1-*b*]thiopyran-1'-ylidene)-9*H*-thioxanthene (6.57)



A mixture of *trans*-**6.56** (14 mg, 31 µmol), methyl-d_3 iodide (3 drops), K_2CO_3 (25 mg, 0.18 mmol) and DMF (1 ml) was stirred for 2h at room temperature. When TLC indicated completion of the reaction, the reaction mixture was poured into water (100 ml) and ethyl acetate (100 ml) was added. The organic layer was washed with water (4x 100 ml), dried (Na_2SO_4) and then all volatiles were removed under reduced pressure to give a yellow oil. This oil was purified by column chromatography (SiO_2, heptane:ethyl acetate, R_f= 0.42) to give *cis*-**6.57** as a white solid (13 mg, 28 µmol, 89%). According to ^{1}H NMR, the *cis*-*trans* ratio of the product was 80:20. The *trans*-**6.57** was prepared from *cis*-**6.56** and (8 mg, 18 µmol) and was obtained as a white solid (6 mg, 13 µmol, 72%). According to ^{1}H NMR, the *cis*-*trans* ratio of the product was 17:83.; ^{1}H and ^{13}C NMR spectra were identical to the previously synthesized all hydrogen analogue **6.2**, except for the deurated signal; *m/z* (EI, %) = 471 (M^+, 100); HRMS(EI): calcd. for $C_{29}D_3H_{21}O_2S_2$: 471.1403, found: 471.1410.

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